Behavioural and neural correlates of the Iowa gambling task

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Abstract

The current set of studies aimed to examine reward related learning on the Iowa gambling task (IGT) in younger and older healthy adults as well as patients with brain injury. The studies look at the relationship of reward-based learning, non-reward related rule learning, emotion processes, and executive function abilities. The investigations also examine neural correlates of reward-based learning using voxel-based morphometry (VBM) with brain-injured patients and functional magnetic resonance imaging (fMRI) method with younger healthy adults. No significant age related effects were found on IGT performance. A significant positive association was found for IGT performance and classification of positive valence pictures while controlling for apathy scale scores. Mapping of grey matter correlates of early learning for reward-based learning (IGT) and non-reward related rule learning (BRFS) revealed a similar left frontal pole neural correlate for both tasks and the differential right caudate association for reward-based learning on the IGT. For the fMRI investigation, general decision-making on the IGT in healthy younger adults involved left orbitofrontal cortex, right anterior cingulate, middle and inferior frontal gyrus. Learning in the IGT involved the right cerebellum, left frontal pole, and left caudate. Amygdala involvement was also found.

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Chapter One

General Introduction

1.1 Reward-based learning

Learning to make financial decisions in the real world is based on uncertain and often changing situations that determine the dividends of such decisions. Advantageous decision-making would involve learning from previous experience of rewarding and negative loss incurring outcomes that have an emotional effect on individuals. James and Lange theories states that emotion related psychosomatic experience affects human actions (James, 1894; Lange, 1885), and taking this proposal further the "Somatic Marker Hypothesis" (SMH; Damasio, 1994) suggested that emotional processes that affect autonomic feedback from the body shapes decision-making ability.

The main support of the SMH has been from evidence using a laboratory-based experiment, Iowa Gambling Task (IGT; Bechara, Damasio, Damasio, & Anderson, 1994). This task includes card decks that have different monetary values and the goal is to optimise rewards on the task by not selecting card decks that seem to offer high quick rewards that lead to much higher losses, in preference for card decks that give small amounts of monetary rewards that also incurs much lower losses. This task was first used to assess patients with frontal lobe lesions who have problems in everyday decision-making despite of intact executive function abilities. These patients were found to select more from disadvantageous card decks (Bechara et al., 1994), which Damasio and team have argued is linked to lowered autonomic response in patients with ventromedial prefrontal cortex (vmPFC) as well as amygdala lesion patients before making decisions (Bechara, Damasio, Tranel, Damasio, 1997; Bechara, Damasio, Damasio, Lee, 1999; Bechara, Tranel, Damasio, 2000b). Healthy controls were found to select more from advantageous card decks overall on the IGT and this performance was found to be associated with higher autonomic skin conductance response before risky card selections that

led to overall losses, suggesting that an avoidance strategy to losses was adopted in performance on the IGT (Bechara et al., 1997).

However, a variety of studies using the IGT with different patients groups who do not have localised lesions in the vmPFC have also been found to be impaired on the IGT, such as patients with substance dependence (Bechara & Damasio, 2002; Bechara, Dolan, & Hindes, 2002; Bechara & Martin, 2004), schizophrenia (Sevy, Burdick, Visweswaraiah, Abdelmessih, Lukin, Yechiam, Bechara, 2007), Parkinsons' diesease (Kobayakawa, Koyama, Mimura, Kawamura, 2008), and anorexia nervosa (Tchanturia, Liao, Uher, Lawrence, Treasure, & Campbell, 2007). These findings have raised the question of specificity of the role of the vmPFC and related regions argued in the SMH to be determinant of advantageous decision making. Studies have also reported that some patient groups which were expected to be impaired in decision making show a similar performance on the IGT to healthy controls (Heims, Critchley, Dolan, Mathias, Cipolotti, 2004; Evans, Bowman, Turnbull, 2005). Further, advantageous decision making on the IGT has not always been consistent in healthy individuals (Evans, Kemish, Turnbull, 2004; review: Dunn, Dalgleish, Lawrence, 2006). The basis on which the SMH has been conceived, - measurable physiological state changes, i.e. skin conductance responses (SCRs), as an indicator of emotion related processes that shape decision-making has also been questioned (Tomb, Hauser, Deldin, Caramazza, 2002). In light of the challenging issues surrounding the SMH based on evidence using the IGT, the current research examines reward-based learning in different groups of individuals and the relationship to other cognitive processes, such as emotion related processes, general rule learning ability, and executive function abilities, as well as to ascertain neural associations of reward-based learning in the IGT in relation to neural regions related to general rule learning and emotional processes.

1.2 Somatic marker hypothesis

The SMH was formulated based on observations of brain-injured patients who suffered damage to the medial orbitofrontal cortex (OFC), more specifically the vmPFC, although the authors note that patients' brain lesions were not exclusive to this neural region (Bechara et al., 1994). Problematic decision-making abilities in everyday life despite of normal ability in laboratary-based experiments on executive function was observed in these patients and altered physiological state changes in response to emotional stimuli along with reduced expression of emotion and experience of emotion led the Damasio (1994) to suggest that emotional impairments was leading to disadvantageous decision-making in these patients. Physiological indicators of bodily state changes, labelled as 'somatic markers', was used as a measure of physiological-emotional state, namely skin conductance responses (SCRs). Correlation of higher SCRs before card selections on the laboratory-based experiment involving learning to make advantageous decisions based on rewards and losses, the IGT and more advantageous decisions observed in healthy patients unlike lower SCRs before decision making for vmPFC and amygdala patients who performed poorly on the IGT, led to the argument that emotional state changes before making choices modulates decision-making (Bechara, Tranel, Damasio, Damasio, 1996; Bechara, Damasio, Tranel, Damasio, 1997). Based on the SMH, emotion has been assumed to reflect a homeostasis of the brain and the body in response to external stimuli. During decision-making, physiological changes that occur (such as heart rate, blood glucose, musculoskeletal changes) which constitutes an emotional change, is produced for every option that is available. The emotional indicators for each potential outcome from an option serve as a

signal to the brain that triggers cognitive processes such attention and memory (Bechara and Damasio, 2005). Decision-making is overall explained by the SMH as processes of reasoning on profitability and biological responses to changes to external stimuli (Damasio 1994; Bechara, Damasio, Damasio, 2000; Bechara and Damasio, 2005).

Several brain regions, such as the vmPFC and other subcortical regions have been implicated in processing biological markers that influence decision-making. Damage to the vmPFC, amygdala, insula, anterior cingulate, hypothalamus, striatum, somatosensory cortices, and brainstem nuclei, was predicted to lead to failure in processing biological indicators that determine decision-making (Bechara and Damasio, 2005).

1.3 Iowa gambling task

The IGT (Bechara et al., 1994) is a reward-based learning task where four card deck options with varying amounts of monetary gains and losses presented are selected consecutively from and the gradual change in decision-making behaviour over trials towards to the advantageous card decks would indicate a learning behaviour. The corresponding phasic change in the recorded autonomic responses show increasing differences between SCRs levels for choices from disadvantageous card decks compared to advantageous card decks, suggesting that bodily state changes provide an indicator that guides choices away from disadvantageous card deck selections (Bechara et al., 1996). Reward-based learning on the IGT was initially found to be impaired in patients with specific brain lesions in the ventromedial prefrontal cortex (vmPFC) and subcortical regions such as the amygdala, and their SCRs recordings were reported

to be significantly lower for the time period just before a card selection unlike healthy controls who selected more from advantageous card decks (Bechara et al., 1997; Bechara et al, 1999).

However, there have been inconsistencies in the evidence based on the IGT. A study by Heims and colleagues (2004) found that adults who are unable to produce autonomic responses due nervous system related illness were still able to select advantageously on the IGT. Studies have found also variability in reward-based learning within groups of older healthy adults, (Denburg et al., 2005; Denburg et al., 2006). In healthy younger adults, a higher formal educational background predicted worse learning on the IGT (Evans, et al., 2004). Neuropsychological studies show that patients with vmPFC lesions are impaired in performance on the IGT (Bechara, Damasio, Tranel, & Anderson, 1998; Bechara, et al., 2000; Waters-Wood, Xiao, Denburg, Hernandez, Bechara, 2012; Gläscher, Adolphs, Damasio, Bechara, Rudrauf, Calamia, Paul, Tranel, 2012), however these studies have failed to show in their performance measure used that patients have an impairment in selecting advantageously across the entire IGT. The performance measure used to assess advanategous decision making in these studies only reflect overall number of safe compared to risky card deck selections which does not take into account learning across the whole task (i.e. comparison of final compared to initial block of card deck selections). These issues of patient group learning, differences in performance in healthy adults, and validity of performance indicators on the IGT have yet to be fully addressed.

1.4 IGT and emotional processes

The argument for the SMH is that somatic markers (i.e. physiological indicators related to arousal) as a measure of emotion related processes before a card selection on the IGT is

predictive of more advantageous card deck selections on the task (Bechara et al, 1997; Damasio, 1994). A study by Suzuki and colleagues (2003) has however found that SCRs that are produced in the outcome period after each card selection is more predictive of learning performance that shows improvement across the IGT. Based on these findings, the role of emotion in reward-based learning seems to be related to physiological factors such as arousal that affects card selection decisions. Other evidence has also found that the aspect of valence (i.e. pleasantness or unpleasantness) of emotion is also predictive of more advantageous card selections on the IGT (Northoff, Grimm, Boeker, Schmidt, Bermpohl, Heinzel, et al., 2006). Studies have also argued that factors that can alter this relationship between reward-based decisions and emotional processes can have an influence in decision making behaviour (Loewenstein, Weber, Hsee, Welch, 2001), such as increased risk can have a negative effect on monetary based decisions (Shiv, Loewenstein, Bechara, Damasio, & Damasio 2005), and frequency of outcome (i.e. increased frequency of rewards and losses) shapes reward-based decisions (Horstmann, Villringer, Neumann, 2012).

1.5 IGT, general rule learning and executive function abilities

Studies have also suggested that working memory abilities are closely linked to emotion related processes in decision making (Hinson, Jameson, Whitney, 2002). Interference tasks with high working memory loads have been found to negatively affect decision making on the IGT (Dretsch and Tipple, 2008; Stocco, Fum, & Napoli, 2009). However, a study by Bechara and colleagues (1998) suggest that working memory ability may be differentiated from decision making on the IGT. Further investigation of the likely relationship between learning on the IGT and other executive function abilities, such immediate recall capacity is necessary to

understand the cognitive processes involved in this complex reward learning based decision making task.

General rule learning that does not involve reward processes could also be examined in relation to reward-related learning to ascertain similarities and differences between different types of rule learning. For instance, the Brixton rule learning task is a visual-spatial rule finding test that assesses the ability to learn a rule based on trial and error which has also been found to be impaired in patients with frontal lobe injury (Reverberi, Lavaroni, Gigli, Skrap, & Shallice, 2005). Further neuropsychological investigation of how this ability to learn spatial rules differs from reward-based rule learning task that also depends on trying and testing possible rules would yield interesting findings.

1.6 Neural regions linked to the IGT

Studies using functional neuroimaging based on the blood oxygenation level dependence (BOLD) signal change found significant neural response in the vmPFC, dorsolateral prefrontal cortex (dlPFC), anterior cingulate, and subcortical regions such as the caudate during the performance on the IGT in healthy controls (Fukui, Murai, Fukuyama, Hayashi, Hanakawa, 2005, Lawrence, Jollant, O'Daly, Zelaya, Phillips, 2009; Li, Lu, D'Argembeau, Ng, Bechara, 2010). Similar findings have also been reported in studies using voxel-based morphometry (VBM) to map grey matter correlates of behavioural performance on the IGT (Gansler, Jerram, Vannorsdall, Schretlen, 2012). Previous research with patients found that separate brain regions were involved during the evaluation of choices and choice outcomes, namely the involvement of the vmPFC brain region during the evaluation of choices (Bechara et al., 1997),

and the recruitment of the amygdala during the processing of outcome (Bechara et al., 1999). However, these findings have been based on a performance measure that looks only at overall number of advantageous more than disadvantageous card deck selections which is not indicative of learning behaviour. The neural circuitry involved in reward-based learning on the IGT still remains uncertain.

1.7 Apathy

Apathy is a disorder of diminished motivation that affects every day adaptive behaviour (Marin, Firinciogullari, Biedrzycki, 1991). Clinical studies have found that motivational loss as a result of apathy reduces quality of life, since individuals' personal effectiveness in everyday tasks is affected by debilitating effects on social interactions, medical treatment outcomes, and rehabilitation (Reid-Arndt, Nehl, Hinkebein, 2007; Resnick, Zimmerman, Magaziner, Adelman, 1998). Research has also shown a high prevalence of apathy in various neurological and psychiatric disorders (van Reekum, Stuss, Ostrander, 2005). Similarities in characteristics to other neuropathologies suggest that damage to underlying brain systems could be a major determinant of apathy. However, the brain and behaviour relationship of this phenomenon is still uncertain (Brown and Pluck, 2000). Studies have postulated certain neural circuits could be involved in apathy (Marin and Wilkosz, 2005). Clinical studies have so far postulated on the different roles that neural structures and circuits play in bringing about and maintaining a motivational state, which if affected, results in diminished goal-directed behaviour (Brown and Pluck 2000; Marin and Wilkosz, 2005). The anterior cingulum (AC), nucleus accumbens (NA), ventral pallidum (VP), thalamus, and the ventral tegmental area (VTA) form the core of the neural system

recruited for motivation, and the NA, VP, and thalamus have been suggested to modulate motivation (Marin & Wilkosz, 2005), which Marin (1996) posits would lead to apathy if this circuitry was damaged. Further, studies point to the basal ganglia as the mediating body for information to and from the frontal cortex as part of the motivation circuitry (van Reekum et al., 2005). The striatum regulates dopamine inputs from the pars compacta of the substantia nigra which is essential for motor activity and if damaged could result in Parkinsonian symptoms of inactivity linked to apathy (Brown & Pluck, 2000). These findings suggest that apathy is the resultant effect of intricate interconnections in the motivation neural network which could be further examined to further understand other possible related cognitive impairments such as decreased emotional processing and motivational decision-making impairments.

Marin (1996) posits a construct of apathy that emphasizes on motivation, which refers to the attributes of goal-directed behaviour. The clinical diagnosis of apathy would involve reduced overt behaviour, ideas and emotional responses that are related to goal-making, despite of normal levels of consciousness, mood, attentional capacity, and executive cognitive abilties. Reduced goal-directed overt behaviour could refer to a diminished ability in social interactions, or reduced occupational capacity. Less goal-directed ideas could be the infrequent expression of personal interest or future plans, and lowered emotional reactivity, may be a lack of or inappropriate emotional responses to goals and interests. Overall, patients would seem less emotionally responsive, or express emotions that are not expected in reaction to a particular situation, and would hence seem emotionally indifferent and unable to react to significant life events. All three aspects of overt behaviour, ideas and emotions, would have to be affected for a diagnosis to be made,

with the emphasis on the lack of goal-directed behaviour. However, an alternative definition put forward by Stuss and colleagues (2000) suggest that apathy is the lack of reaction to ones environment which is due to an inability to initiate the necessary actions. The lack of initiation could be manifested behaviourally, emotionally, and cognitively. In addition, Stuss et al (2000) postulates that there are several sub-categories of apathy which is determined by parts of the frontal-subcortical brain circuit affected. In defining apathy as a psychopathological construct, these definitions would enable a more succinct examination of the individual aspects of apathy, and the underlying neural systems involved.

1.7.1 Effects

Individuals with apathy have been described as having flattened emotions, with problems in expressing appropriate emotional responses to events (Marin, 1996). The adverse result of this disorder has a pervading effect, causing problems in socializing, distancing from close ones, and difficulties in meeting the challenges of an occupation, hence leading to the financial and familial burdens for the individual. A study by Reid-Arndt and colleagues (2007) found that following traumatic brain injury, assessments on levels of functionality carried out using the Frontal System Behaviour Scale (FrSBe) was an accurate indicator of a patient's ability to integrate back into society. Based on the evaluation using the FrSBe, the study found that substantial numbers of TBI patients had problems in occupational, familial, and emotional aspects of their lives that prevented community involvement.

Other outcomes of apathy can also be problematic for both patients and carers. A study found that having apathy prior to the start of rehabilitation for various medical conditions, such as stroke, was correlated to functionality after treatment (Resnick, et al., 1998). Patients with Alzheimer's disease (AD) who are apathetic have also been found to suffer more rapid cognitive losses than patients who are not apathetic (Doody, Massman, Mahurin, et al., 1995). These findings show a relationship between apathy and poor illness outcome, and points to the need to further understand the determinants of this disorder, which could lead to better treatment outcome of various illnesses.

1.7.2 Prevalence

An extensive study carried out by van Reekum and colleagues (2005) showed a high prevalence of apathy in neurological disorders. With the use of an assessment tool, the Apathy Evaluation Scale (AES) a prevalence of apathy of 46.4% of 28 patients was found in traumatic brain injury (TBI) patients (Andersson, Krogstad, & Finset, 1999). Other studies examined the frequency of apathy in patients with Alzheimer's disease (AD) using another commonly used assessment tool, the Neuropsychiatric Inventory (NPI) and found a prevalence rate of 65.1% out of 261 AD patients (Benoit, Dygai, Migneco et al., 1999; Aharon-Peretz, Kliot, Tomer, 2000; Kaufer, Cummings, Christine, et al., 1998). Similar patterns of prevalence have also been found in other patient groups with conditions that also involve cortical structures. More about the neural underpinnings of apathy could perhaps be suggested from the different frequency rate of apathy found in patients with lesions in different frontal regions. For instance, five of seven patients with bilateral ventromedial prefrontal lesions were found to be apathetic, while 3 out of 14 patients

coping with nonmedial prefrontal lesions were found to have apathy (Barrash, Tranel, and Anderson, 2000). The prevalence of apathy reported by these studies in various pathologies concerning cortical areas suggests a link of neural areas, particularly frontal regions, to the phenomenon of apathy.

A high frequency of apathy has also been reported in patients with pathologies linked to subcortical structures. Studies which used the Neuropsychiatric Inventory and other measures to assess the rate of apathy in patients with focal lesions of the globus pallidum, caudate, putamen, found these patients to be apathetic (van Reekum, et al., 2005). Other conditions which involve frontal as well as subcortical regions such as depression, had a prevalence rate of 53.3% out of 30 patients (Marin, Firinciogullari, Biedrzycki, 1991). Further, it was revealed that the frequency of apathy in myotonic dystrophy, which affects the central nervous system, was higher than the rate in Charcot-Marie-Tooth disease, which affects peripheral nerves (Rubinsztein, Rubinsztein, Goodburn, 1998). Other studies have also found a prevalence of apathy in patients who have suffered a stroke, the rate was 34.7% of 190 individuals (Okada, Kobayashi, Yamagata, Takahashi, Yamaguchi, 1997; Starkstein, Fedoroff, Price, Leiguarda, Robinson, 1993). These findings show a prevalence of apathy in neuropathologies that are linked to subcortical regions as well as conditions involving both cortical and subcortical regions, which may be linked to other cognitive processes that have been associated with brain injury such as reward based learning.

1.8 Objectives of studies

This set of studies aims to examine: 1.) age effects in reward-based learning on the IGT and related emotion processes based on valence classification, as well as apathy; 2.) similarities and differences between reward-based learning on the IGT and non-reward based learning in patients with brain injury in terms of behavioural correlates with executive function abilities and emotion related processes linked to valence, as well as mapping of grey matter correlates of behavioural performance to ascertain the neural associations for reward-based learning on the IGT and non-reward based learning; 3.) neural regions involved in reward based learning on the IGT in healthy young adults and the relationship between emotion related neural regions of the same group of participants with their learning on the IGT. Overall these investigations aim to examine the potential differences in performance on a reward-based rule learning task, the IGT in younger and older healthy adults as well as patients with brain-injury, and the relationship with cognitive processes that are related to emotion, non-reward based rule learning and executive function abilities as well as examine associated neural regions of reward related learning based on the IGT.

Chapter 2

Effects of age on reward-related learning and valence-based emotional processes

2.1 Introduction

Studies have suggested that age-related cognitive decline influences reward-based learning in older adults (Denburg, Cole, Hernandez, Yamada, Tranel, Bechara, & Wallace, 2007), however there are also evidence to suggest that reward learning is intact in older persons (Gansler, Jerram, Vannorsdall, & Schretlen, 2012). Age-related effects have also been claimed to influence emotion processes that are related to valence (i.e. pleasantness or unpleasantness; Grühn & Scheibe, 2008), however findings have also shown that positive valence of emotion do not differ between younger and older adults (Wood & Kisley, 2006). Apathy which is an emotion related disorder that results in lower emotional response and poorer decision-making in everyday life, was also suggested to differ between age groups (Clarke, Ko, Lyketsos, Rebok, Eaton, 2010), however much of the focus on apathy studies has been on aging or patient groups and further research to ascertain the effects of apathy on reward-based learning in younger adults in comparison with older participants has not been carried out. This study aims to examine reward-based learning between younger and older adults, and the relationship with valence-based emotion processes as well as apathy.

Age-related differences have been suggested to influence decision-making on the widely used Iowa gambling task (IGT; Bechara, Damasio, Damasio, & Anderson, 1994). The study by Denburg and colleagues (2005) found a significant interaction between age and number of advantageous card deck selection across the entire IGT. The same study also examined a subgroup of older participants who learned on the IGT in comparison with younger participants' performance and found that there was no longer the significant interaction for age and number of advantageous compared to disadvantageous card deck selections over the entire task (Denburg, et al., 2005). A follow-up study from the same

team focusing on a different sample of older participants found a significant interaction for group (i.e. participants who learned on the IGT compared to those who did not learn) and overall number of advantageous compared to disadvantageous card deck selections across the whole task (Denburg, Recknor, Bechara, Tranel, 2006). These findings suggest that learning ability on the IGT varies within the older age group. Further, in the study by Gansler and colleagues (2012) decision-making on the IGT in older adults, reported that participants were able to improve significantly over the task. A study using a 2 deck version of the IGT, with constant gains and infrequent penalties, found that both groups of younger and older participants gradually selected more from advantageous cards decks as the task progressed, showing that learning was achieved by both age groups (Kovalchik, Camerer, Grether, Plott, & Allman, 2005). These findings on reward-based learning abilities in older adults are inconclusive, and further investigation to ascertain the similarities and differences in reward-based learning between younger and older adults, in terms of emotion-related processes would help to further understand possible differences that are age-related.

Findings from previous studies on reward-based learning and emotion valence processes between older and younger adults have also been mixed. A study using meta-analysis of 29 previous studies that compared younger and older participants' preferential selections on tasks that involve a gains and loss framework, found no distinct differences between both age groups across studies (Mata, Josef, Samanez-Larkin, & Hertwig, 2011). Evidence on valence ratings of emotive images showed no significant difference in valence ratings for positive images between younger and older age groups, although significantly higher negative valence ratings for emotive images was found for older adults (Wood & Kisley, 2006, Massavelli, 2010). However, a study by Grühn and Scheibe (2008) also

examined valence ratings on emotive pictures and found significantly higher response ratings for older compared to younger adults for both positive and negative valence ratings. The findings on emotion processes that are linked to valence are therefore inconclusive and require further research to ascertain possible differences in emotion-related processes in older adults. Further, these findings also suggest that the relationship between reward-based learning that involves decision-making based on gains and losses and emotion processes related to valence may not be fully understood. Previous studies involving brain-injured patients suggest that valence-related emotion processes prior to a disadvantageous card selection (i.e. negative reinforcements) are necessary to lead future card selections away from the overall losing decks for successful decision-making on card decks (Bechara, Damasio, Tranel, Damasio, 1997; Bechara, Tranel, Damasio, 2000), and other evidence in healthy younger adults also suggest that valence-based emotion outcome of disadvantageous card selections influences future decisions on card decks (Suzuki, Hirota, Takasawa, & Shigemasu, 2003). Further investigation of the effects of valence–based emotion processes on reward-based learning for comparison between different age groups is still necessary.

Apathy which is an increasingly reported clinical condition where there is the lack of emotional responsiveness, as well as the absence of goal-oriented thoughts and behaviour (Marin & Wilkosz, 2005), which could be also be linked to reward-based learning and emotion-related processes in both younger and older adults. One study using the 20-item General Health Questionnaire (GHQ; Goldberg, 1978) which include statements such as "managing to keep yourself busy and occupied/ getting out of the house as much as usual/ able to enjoy your normal day-to-day activities as much as usual", found that age was

related to higher apathy scores in older adults, and further higher apathy levels was also associated with lower scores on the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) and action-directed abilities in day-to-day activities (Clarke, et al., 2010). Higher apathy scores have also been linked to poorer cognitive abilities assessed by the Boston Naming and Animal Fluency tests, as well as the Trail Making Test-Part B in healthy older adults (Onyike, Sheppard, Tschanz, et al., 2007). Apathy was also found to be correlated with behavioural performance on a delayed-intention task in older adults (Esposito, Rochat, Van der Linden, Van der Linden, 2012), which suggests implications of apathy on various cognitive abilities. There was been no study known to have examined the effects of apathy on reward-based learning between younger and older healthy adults, which the current study carried out.

This study aims to examine reward-based learning in adults from younger and older age groups, concurrently with emotion processes related to valence and apathy. This study predicted that there may be no differences between younger and older adults in selecting advantageous (also called 'safe') compared to disadvantageous (also called 'risky') card selections for overall (final minus first block of 20 card selections) and early (second minus first block of 20 card selections) learning performance on the IGT. However, emotion processing was predicted to differ between the older and younger age groups only for both number of emotive pictures categorised as having a negative emotion valence (i.e. unpleasantness) and positive emotion valence (i.e. pleasantness). Apathy scale scores was also expected to be significantly higher in healthy older participants compared to younger controls. Further, in this study the relationship between reward-based learning on the IGT (i.e. overall and early stages) and emotion processes (i.e. positive and negative valence) was

explored for both age groups. Similarly, a possible association between reward-based learning on the IGT and apathy scale scores was also examined in younger and older adults.

2.2 Methods

2.2.1 Participants

Sixteen older adults (4 females) with no medical or neurological conditions were recruited. The age range of the older adults was between 55 to 82 years of age (mean=69.25, SD= 6.89). The inclusion criterion was anyone 55 years of age and above. The exclusion criterion was any history of a neurological or psychiatric condition. No one was excluded from the study based on this criterion. Nineteen young adults between the age of 18 to 20 (mean=18.9; SD=0.46) were also recruited for the study as younger controls. The inclusion criterion for this group of participants was anyone between the age of 18 to 23 years of age. The exclusion criterion for this group was familiarity with the Iowa gambling task and any history of a neurological condition, and one individual was excluded based on this criteria. On the picture-categorization task only 14 of the 19 younger adults were tested, this is due to technical issues on the testing computer used for this study that prevented 5 participants' data on this task to be collected. Participants from both age groups gave informed consent to take part in the study. Those from the older age group were paid £6 for their participation, while participants from the younger age group were given course credits for taking part. Both groups were aware that they were not paid based on their performance on any of the tasks in this study.

2.2.2 Procedure

2.2.2 1 IGT

The experiment was a computerized version of the IGT (Bechara et al., 2000b) originally adapted for use in an fMRI investigation (Lawrence et al., 2009). The version of the IGT aimed to simulate decision-making scenarios which involve the assessments of future monetary gains by forgoing immediate rewards that accrue overall losses. Participants were individually tested and had to choose 100 cards from 4 separate decks, labelled A B C D (Figure 2.1).

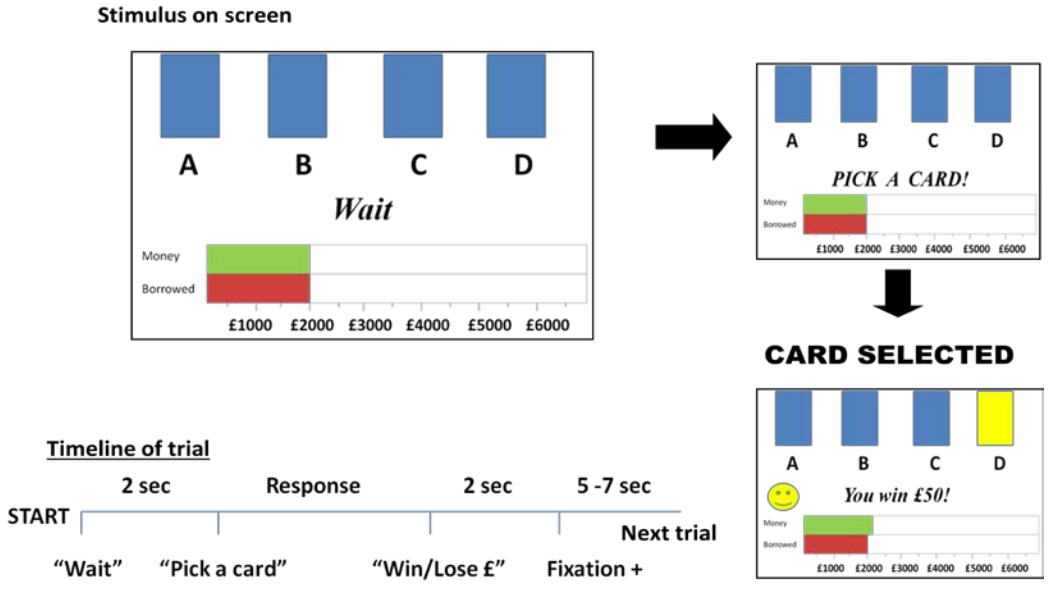


Figure 2.1 Example of an experimental trial on the IGT and timeline.

The aim of the task was to win as much money as possible. In the instructions (Appendix 1), it was explained to the participants that they could chose from any card deck but that they could win or lose money from each of the decks. They were also told that "It is important to know that the computer does not make you lose money at random. However, there is no way for you to figure out when or why you lose money. All I can say is that you

may find yourself losing money on all of the decks, but some decks will make you lose more than others. Even if you lost a lot of money, you can still win if you stay away from the worst decks." These instructions are the same as the computerized IGT task used in the study by Lawrence and colleagues (2009).

Participants' winnings were displayed on a green bar which indicated the amount of money they had won, and a red bar which indicated the amount of credit they had borrowed to play the game. Decks A and B were the risky decks, where there were higher winnings (£190, £200, £210) and higher losses (£240, £250, £260). For safe decks C and D, there were lesser winnings (£90, £100, £110) and even lesser losses (£40, £50, £60). Choosing more from decks C and D would result in overall gains. Hence, task performance is determined by the number of selections from the safe card decks (C and D) over the number of cards chosen from the risky card decks (A and B), i.e. (C + D) – (A + B). Overall learning of the task rules is shown by more card selections from the safe card decks in a later stage of the task compared to an earlier stage of the task. For that reason the trials are divided to five blocks, with 20 trials in each. Early learning is computed by comparing the performances on the 1st block (i.e. trails 1 to 20) to the 2nd block (trials 21 to 40), while slower learning is computed by comparing responses of the 1st block to the final 5th block (trials 81 to 100). The game was a simulation of decision-making only as participants were not paid according to their task performance. However, anecdotal observations suggested that despite the lack of direct monetary reward majority of the participants were highly engaged at the task, and showed an alert emotional response to winning and losing outcomes of their choices.

Modifications carried out by Lawrence and colleagues (2009) on the original computerized version of the IGT are as follows:

1.) Card decks A and B in this version of the IGT were similar to deck A of the original IGT, in terms of reward and losses contingencies (overall loss of £250 over 10 card selections), while card decks C and D were similar to deck C of the original task, in terms of gains and punishment contingencies (overall gain of £250 over 10 card selections). The card decks had a similar ratio of wins to losses frequency (50/50) as card decks A and C of the original IGT. This change allowed for greater statistical power during analysis of the differences between the safe and risky card deck selections and further after performance on the IGT participants reported differential preferences between decks A and B, as well as decks C and D.
2.) Either a 'win' or 'lose' for each trial was presented to participants for the card deck selected. The amount of money won or loss on each card deck selection was the same as overall amounts won or lost on the original IGT. This modification meant that there was no calculation involved in working out the overall reward and penalty on each card selection.
3.) Participants were also alerted to an imminent decision when card decks reappeared after an inter-trial interval, i.e. "wait" was presented 2 seconds before a card selection was expected, i.e. "Pick a card". There was also a time limit of 3 seconds to select a card deck before participants were told it was "too late" to respond. Inter-trial intervals were varied between 5-7 seconds, which consisted of a fixation cross.

Each trial lasted between 10-12 seconds. Card selections were followed immediately by the reinforcement outcome (i.e. a win or a loss of money) for 2 seconds. The duration of the

display of the fixation cross was adjusted according to the participants' reaction time, so as ensure that the whole task lasted for 1321 seconds (22.02 min). 10 visual motor control trials were included at the end of the 100 trials of the experiment task, where participants were instructed to pick a specific card from 4 card decks displayed, labelled E, F, G, or H, by pressing one of four buttons that corresponds to the position of the card across the screen. The control trial began with the instruction "Pick card E" instead of "Pick a card", and participants were asked to respond accurately within 3 seconds and that the correct response would be recorded. After a response, participants would be given the feedback that "You picked a card" for a duration of 2 seconds. The green bar at the bottom of the screen did not increase or decrease during these trials. The colour of the decks E, F, G, H was different from decks A, B, C, D. Other appearance and structure of trials of the control task was the same as trials of the experiment task.

Participants were all given the same instructions and 6 practice trials before starting the actual task. The 6 practice trials consisted of 2 trials of the control task followed by 4 trials from the experiment task. The practice trials were to familiarise participants of the appearance and layout of the response buttons of the task.

2.2.2.2 Picture categorization task

The task was run on Eprime version 1.1. Participants viewed a series of emotive images from the International Affective Picture System (IAPS; Lang, Bradley & Cuthbert 1997). The images were selected based on the IAPS normative ratings computed based on a 9-point rating scales of valence (i.e. 1-unpleasant to 9-pleasant) and arousal (i.e. 1-calm to

9-excited). The 29 selected stimuli were grouped into three emotional categories attempting to emphasize difference in valence but all with relative high arousal: 1) positive (average valence rating of 7.6 [SD 0.5); 2) neutral (valence 5.9 [SD 0.7]); and 3) negative (valence 3.36 [SD 0.6]). Pictures were presented in colour and viewed on a screen resolution of 1024 x 768 pixels. The images were presented one by one, in randomised blocks of positive, negative and neutral images, to ensure presentation of the different categories of images were counterbalanced. Each image was presented for 6 seconds followed by an inter-trial interval of 12 seconds during which participants could still make a response. The whole picture categorizing task lasted for 540 seconds (9mins).

Participants categorised each stimulus on whether it evoked in them a positive, negative or neutral feeling. This was done by pressing a button for each category using an ordinary computer keyboard labelled 'happy', 'neutral', or 'sad' (Figure 2.2). Participants were instructed to categorise the images as 'happy' if the picture made them feel pleasant, or 'sad' if the pictures made them feel unpleasant, and if the image did not evoke in them any feeling of pleasantness or unpleasantness, i.e. it is just an object or for example a building, they were asked to give the response 'neutral'. This simple valence categorization task was used as opposed to rating valence over a long continous scale as pilot testing in the same research laboratory suggested that some people find it more difficult to use a continuous rating scale. For each participant we then derived a negative and a positive emotive score by totalling the number of times they categorised a picture as 'sad' or 'happy' rather than 'neutral'. Images included objects as well as persons within social situational contexts.

A B C

Figure 2.2 Examples of images with negative (A) and positive valence (B), as well as a picture with neutral content.

2.2.2.3 Apathy scales

Apathy was assessed by the Apathy Evaluation Scale (AES self-rated; Marin, Biedrzycki, Firinciogullari, 1991; Appendix 2) and the self-rated Lille apathy rating scale (LARS; Sockeel, Dujardin, Devos, Deneve, Destee, Defebvre, 2006; Appendix 3). The AES is a measure of everyday adaptive behaviour, which includes 18 statements. These statements on the AES self-rated version are presented in the first person narrative (e.g. 'I am interested in learning new things'; 'Getting things started on my own is important to me'; 'Seeing a job through to the end is important to me'). Each statement is rated on a 4-point Likert scale, which was presented as (Not at all, Slightly, Somewhat, A lot). The scores ranged from 18-72. A score of AES that is above or equal to 37 is considered to reflect the presence of an apathetic condition (Marin et al., 1991).

The LARS is an adaption of the AES and is argued to be more accurate in measuring apathy as behaviour (Sockeel, Dujardin, Devos, Deneve, Destee, & Defebrve, 2006; Appendix 3). This scale takes into account four separate behavioural components (intellectual

interest, self-awareness, emotional responsiveness, and self-initiative) which are important for assessing apathy. There are 33 questions, first 2 questions are open-ended (e.g. what do you do during the day? Tell me about your day-to-day life; what to you like to do to keep yourself occupied?) The scoring is based on the time taken to reply, number of needed prompts, and number of activities (2, no reply; 1, reply after prompting; 0, spontaneous reply but after some time; -1, immediate reply with one activity mentioned; -2, immediate reply with several activities mentioned). Further, the number and variety of activities reported is scored based on number of activities reported, if prompting was needed, and if there is a detailed description of a normal day varies over the week/year (2, none; 1, one activity but prompting needed to obtain another; 0, several activities mentioned; -1, detailed organisation of a typical day but everyday follows the same schedule; -2, detailed organisation of a typical day but the reply shows that the activities change according to the day of the week or the time of year). The other 31 questions are 2-force choice statements about oneself (e.g. In general, do you decide to do things or does someone have to push you a little?) and scores are given depending on apathetic nature of the reply (e.g. I have to be pushed [score of 1]; Non-applicable or non-classifiable reply [score of 0]; I decide to do things myself [score of -1]). Scores from all 33 questions are added, and the cut off score on the LARS is more than -16 points to indicate a likelihood of an apathetic condition (Sockeel et al., 2006).

2.2.3 Statistical Analysis

T-tests were carried to ascertain differences between participant groups. Repeated-measures ANOVA for participant group and blocks of card selections on the IGT was also

performed. Correlation analyses of behavioural performance on the IGT, picture-categorization task, as well as scores on the two apathy scales were carried out.

2.3 Results

2.3.1 Behavioural performance

Table 2.1 presents a summary of behavioural and demographic data of both older and younger adults on the IGT, picture categorization task, and apathy scales.

Table 2.1 Demographics and behavioural data of older adults (n=16) and younger controls (n=19) for mean scores on the IGT, picture categorising task, and apathy scales.

	Older adults [mean(SD)]	Younger controls[mean(SD)]	Statistics [t(33) value)	Confidence level (95%CI)
Age	69.25 (6.89)	18.9 (0.46)	-31.84	-53.57 to -47.13
Education	3.25 (1.13)	3 (0)	1.24	-0.22 to 0.85
Gender (M/F)	12/4	1/18		
IGT				
Block 2-1	3.68 (7.3)	0.37 (6.36)	-1.44	-8.01 to 1.38
Block 5-1	3.06 (10.03)	2.95 (7.43)	-0.04	-6.13 to 5.9
Motorcontrol	8.75 (1.44)	9.16 (0.9)	1.02	-0.4 to 1.22
ExpTrials RT (ms)	779.29 (267.8)	723.14 (183.6)	-0.73	-212 to 99.7
ConTrials RT (ms)	1494.56 (290.1)	1103.64 (318.8)	3.06*	-602.2 to -179.6
Apathy scales				
AES – self	25.13 (5.91)	25.58 (4.96)	0.25	-3.28 to 4.18
LARS	-30.31 (4.5)	-30.42 (2.48)	-0.9	-2.56 to 2.34
IAPS task		*(n=14)*		
Positive rating	12.0 (4.31)	10.64 (2.56)	-1.03(28)	-4.06 to 1.34
Negative rating	6.56 (2.9)	7.79 (2.19)	1.29	-0.72 to 3.17

$p < 0.05$

2.3.1.1 IGT performance

Older participants had 87.5% accuracy on the motor-control task, while younger participants had 91.6 % accuracy on the control trials although this was not found to be significantly higher than the older age group. No significant difference was found for overall and early learning between both groups. Repeated-measures ANOVA for performance over 5 blocks of the IGT in both groups, showed a significant effect for block ($F[4,132] = 2.81$; $p < 0.05$), although no interaction with age group was found ($F[4, 132] = 1.97$; $p > 0.05$). A within-subjects comparison over blocks of both groups together showed that performance improved along a linear trend ($F [1, 33] = 4.81$; $p < 0.05$). Figure 2.3 shows the number of safe minus risky card deck selections for the 5 blocks of 20 card selections on the IGT for younger and older participants.

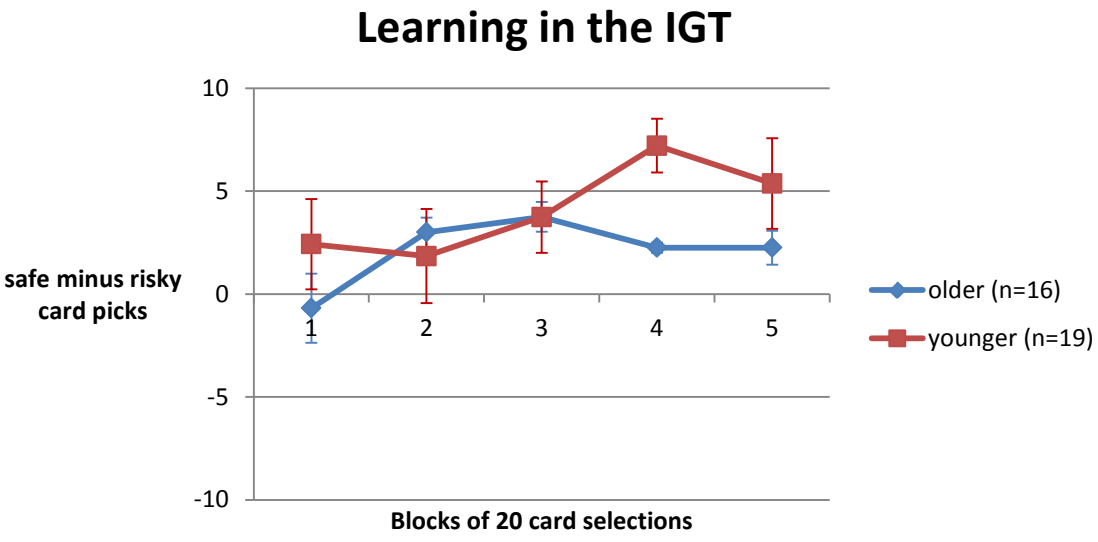


Figure 2.3 Learning over blocks of 20 card selections on the safe minus risky index for older and younger groups.

2.3.1.2 Picture categorising task

Out of the 29 pictures shown, older participants categorized emotive images as having positive valence between 2 to 18 number of times (mean 12.0 ±SD: 4.31). The number of times older participants categorized the images as having negative valence was between 1 to 11 number of times (mean 6.56 ±SD: 2.9). Participants in the younger adult group categorized images as having positive valence between 6 to 14 number of times (mean 10.64 ± [SD] 2.56), as well as grouping images as negatively valence between 2 to 11 number of times(mean 7.79 ± [SD] 2.19) of the 29 pictures viewed. There was no significant difference between numbers of pictures categorised as having a positive or negative valence between both age groups, though on average in comparison to younger participants, the older age group classified more pictures as being positive and less pictures as being negative.

2.3.1.3 AES and LARS

Older participants' scores on the AES self-rated scale were between 18 to 39 (mean 25.13 ±SD: 5.91), for the possible range of 18 to 72. Only one participant was considered apathetic on this scale. For the LARS questionnaire, older participants had scores between -36 to -16 (mean -30.31 ±SD 4.5), within the range of -36 to 36. One participant was also found to be apathetic based on the LARS (although this was not the same individual with a high apathy score on the AES). For younger participants' scores on the AES were between 20 to 38 (mean 25.58 ±SD: 4.96), and one participant was considered to be apathetic on this scale. Scores on the LARS for the younger age group was between -34 to -25 (mean -30.42

±SD: 2.48), however no younger participant was found to have high apathy scores on this scale. No significant difference was found between older and younger adults on both apathy scale scores.

2.3.2 Statistical Analysis

Collapsing scores from both older and younger age groups, partial correlation analysis was carried out between learning performance on the IGT and scores on the picture-categorization task controlling for apathy scale scores. There was significant positive association between early learning and number of images categorised as having positive valence, while partially out effects of apathy based on the AES ($r = 0.37$, $p < 0.05$) and LARS ($r = 0.47$, $p < 0.05$; Table 2.2). However no significant correlation was found for early learning and number of pictures categorised as negatively valence, as well as for overall learning and scores for both positively and negatively categorised images, while restricting the effects of apathy based on AES and LARS.

For the older participant group, there was significant positive correlation between overall and early learning index ($r = 0.55$, $p < 0.05$; Table 2.3). However, education was not found to be significantly associated with both overall and early learning (block 5 minus block 1: $r = 0.24$, $p > 0.05$; block 2 minus block 1: $r = 0.12$, $p > 0.05$). Further, number of pictures categorised as having positive valence was not found to be correlated with learning on the IGT (block 5 minus block 1: $r = -0.16$, $p > 0.05$; block 2 minus block 1: $r = 0.39$, $p > 0.05$), and similarly for number of images considered as having negative valence was not shown to be correlated with IGT performance (block 5 minus block 1: $r = -0.18$, $p > 0.05$; block 2 minus

block 1: r = 0.09, p > 0.05). No significant relationship was found for learning on the IGT and AES scores (block 5 minus block 1: r = -0.07, p > 0.05; block 2 minus block 1: r = 0.12, p > 0.05) as well as LARS scores (block 5 minus block 1: r = 0.04, p > 0.05; block 2 minus block 1: r = -0.05, p > 0.05). There were no significant correlations between number of images categorised as having positive or negative valence and apathy scale scores on both the AES and LARS.

For the younger age group, significant positive correlation was also found between overall and early learning on the IGT (r = 0.87, p < 0.005; Table 2.4). Number of images categorised as positively valence had a significant positive association with both learning indices (block 5 minus block 1: r = 0.67, p < 0.005; block 2 minus block 1: r = 0.69, p < 0.005). However, there was no significant relationship between number of images considered as having negative valence and learning on the IGT (block 5 minus block 1: r = 0.32, p > 0.05; block 2 minus block 1: r = 0.34, p > 0.05). A significant negative correlation between scores on the AES and early learning was found (r = -0.61, p < 0.05), although there was no significant association with overall learning (r = 0.41, p > 0.05). Further, no significant correlation was reported for scores on the LARS and IGT performance (block 5 minus block 1: r = -0.06, p > 0.05; block 2 minus block 1: r = -0.49, p > 0.05). There was also no significant association between learning on the IGT and HADS anxiety subscale (block 5 minus block 1: r = -0.14, p > 0.05; block 2 minus block 1: r = 0.04, p > 0.05), as well as with the HADS depression subscale (block 5 minus block 1: r = -0.44, p > 0.05; block 2 minus block 1: r = -0.42, p > 0.05). Further significant positive correlation was found between scores on the AES and LARS (r = 0.57, p < 0.05). No significant relationship was found for AES scores and

picture categorization scores (positive valence: r = -0.33, p > 0.05; negative valence: r = 0.09, p > 0.05).

Table 2.2 Partial correlation between IGT learning and picture-categorization task, controlling for apathy scale scores (Pearson correlation coefficients; n= 30)

Control variable		IGT B2-1	IGT B5-1
AES	IAPS-Pos	0.37*	0.06
	IAPS-Neg	0.2	-0.2
LARS	IAPS-Pos	0.47*	0.13
	IAPS-Neg	0.21	0.00

** p < 0.05*

Table 2.3 Correlations of participants from the older age group on scores from the IGT, picture-categorization task, and apathy scale scores (Pearson correlation coefficients; n=16)

	Education	IGT B2-B1	IGT B5-B1	IAPS –Pos	IAPS-Neg	AES	LARS
Age	-0.04	-0.19	-0.23	-0.06	-0.12	-0.11	-0.12
Education	1	0.12	0.24	-0.07	-0.35	0.16	0.02
IGT B2-B1		1	0.55*	0.39	0.09	-0.12	-0.05
IGT B5-B1			1	-0.16	-0.18	-0.07	0.04
IAPS-Pos				1	0.36	-0.13	0.48
IAPS-Neg					1	-0.2	0.19
AES						1	0.42

*p <0.05

Table 2.4 Correlations of younger age group controls for scores on the IGT, picture-categorization task, and apathy scale scores (Pearson correlation coefficients; n=14)

	IGT B2-B1	IGT B5-B1	IAPS –Pos	IAPS-Neg	AES	LARS
Age	0.33	0.33	0.11	-0.43	-0.63	-0.44
IGT B2-B1	1	0.87**	0.69**	0.34	-0.61*	-0.49
IGT B5-B1		1	0.67**	0.32	-0.41	-0.44
IAPS-Pos			1	0.26	-0.33	-0.36
IAPS-Neg				1	0.09	-0.39
AES					1	0.57*

*p <0.05; **p <0.005

2.4 Discussion

Overall and early learning was achieved by both age groups. Younger and older participants learned across the entire IGT showing a linear improvement over the task, supporting previous studies that found reward-based learning on the IGT to be intact in older adults (Gansler et al., 2012) as well as supporting other studies which reported no age effects for learning over the IGT (Kovalchik et al., 2005). However, the current findings are unlike a previous study which found a significant effect of age on selecting more advantageous than disadvantageous card decks over blocks on the IGT (Denburg et al., 2005). This could be explained by individual differences in samples within the healthy older population as well as the measure of performance that assesses learning across the stages of the IGT which the study by Denburg and colleagues (2005) did not take into consideration. This finding shows that reward-based learning to be intact in older samples although learning performance could vary within an older healthy population.

Classification of visual emotional stimuli such as the IAPS pictures based on emotion valence were also found not to differ between younger and older participants. This is unlike previous studies that examined valence ratings of IAPS pictures, which showed that negative valence ratings on IAPS images was significantly higher in older adults compared to younger participants and positive valence ratings for another set of IAPS pictures to be also significantly higher for older participants (Grühn & Scheibe, 2008). However, there have also been studies which found that positive valence ratings did not differ between age groups (Wood & Kisley, 2006; Massavelli, 2010). A possible difference in findings could be due to the use of categorization of emotional pictures rather than to base on valence ratings. Apathy scale scores on both the AES and LARS between older and younger participants were

also similar. No other study has compared apathy scale scores between younger and older healthy adults so this study shows a novel finding in the comparison of apathy between different age groups. The findings from emotional processing and apathy scale scores both show that there are no age effects on emotion related cognitive processes in healthy adults.

Significant positive relationship was found between early learning on the IGT and number of IAPS pictures categorised as positive in valence while partialling out effects of apathy based on the AES and LARS. This result was based on the combined behavioural performance of older and younger participants. This suggests that reward-based learning in the early stages of the IGT (i.e. 21st to 40th card selection versus 1st to 20th card selection) is positively related to positive reinforcements (i.e. rewards), and that higher apathy scale scores affects performance on the IGT. This finding is unlike previous studies which suggest that emotion experience from losses on disadvantageous card deck selections guide choices away to the more advantageous card decks (Bechara et al., 1997; Suzuki et al., 2003), and shows that reward-based learning on the IGT is predicted by positive emotions in younger and older adults. The finding also shows that apathy influences reward-based learning, which supports previous studies showing that apathy is related to poorer cognitive abilities (Clarke et al., 2010; Esposito, et al., 2012; Onyike et al., 2007). For the younger control group, overall and early learning on the IGT was also found to be significantly positively associated with number of pictures categorised as positively valence, although a mild positive relationship between reward learning and classification of negative valence pictures was also found. Further, mild negative associations between reward based learning and apathy scale scores were also reported. This is unlike the older adult group, where only mild positive associations between early learning and classification of positive and negative

images were found, although non-significant negative relationships were found between overall reward learning and categorization of positive and negative valence images. This finding shows a possible difference between the age groups on overall reward-based learning and emotion-related processes, suggesting that younger participants continue to recruit positive reinforcements in learning even after the early stages of learning unlike older adults, although this does not seem to have differential effects on learning in the IGT. Another possible suggestion that these findings show is that emotion related processes have more effect on reward-based learning in younger participants. Other samples of the population, such as patients with brain-injury who might have impaired abilities in recruiting emotion feedback for making successful reward-related choices could also be examined on reward-based learning in the IGT in relation to emotion related cognitive processes as well as executive function abilities which might be recruited in learning to make advantageous decisions.

Overall the findings suggest that there are no age-related effects on reward-based learning and emotion processes related to valence. Further, apathy was also found to be unrelated to age affects. However, significant associations between early learning on the IGT and number of IAPS images categorised as positive was found while controlling for effects of apathy, suggests that reward-based learning for both younger and older healthy adults is related to emotional processing and affective disorders such as apathy. Further investigation based on valence ratings could perhaps be used to assess emotion-related processes, and arousal as well as dominance aspects of emotional processing could be further examined in healthy older adults.

Chapter 3

Differential cognitive systems in rule learning: behavioural and neural correlates of two neuropsychological assessment tools.

3.1 Introduction

Rule learning in a clinical set up is frequently assessed using two types of tests: a reward related learning task - Iowa gambling task (IGT; Bechara, Damasio, & Anderson, 1994), and a non-reward related learning tasks – such as the Brixton Spatial Anticipation test (Shallice & Burgess, 1991) and the Birmingham rule finding and switching task (BRFS; Humphreys, Bickerton, Samson, Riddoch, 2012). These tasks are frequently used as neuropsychological tests and both types of tasks (reward and non-reward based) involve working out rule patterns and the application of these rules to decide on a subsequent action. Thus the two types of tasks require similar but also dissociated cognitive processes. For instance, both types of learning tasks often include an exploratory learning phase. Unlike other cognitive tasks, in a rule learning task knowledge of all decision options need to be gathered through experience, rather than explicitly provided. However, in reward and non-reward based learning tasks also differ in the cognitive processes involved. For example, differences between types of learning are likely to arise due to differential involvement of reward related processes, reasoning, as well as memory. The aim of this study is to examine, the similar and dissociable cognitive components of reward and non-reward based learning using a neuropsychological approach and function-lesion mapping. In addition, the effects of emotion related processes and executive function abilities were also examined that could potentially be involved in both forms of rule learning tasks: that are reward-related such as the IGT and non-reward related like the BRFS.

3.1.1 Rule learning in reward related and non-reward based tasks

Neuropsychological studies suggest that the two types of rule learning occur in stages (Bechara, Damasio, Tranel, Damasio, 1997; Crescentini, Seyed-Allaei, De Pisapia, Jovicich, Amati, Shallice, 2011). In the initial stage of learning in both tasks, trial and error selection of options available is necessary to work out the expected outcomes from selected options. This is followed by a second stage of testing out a possible rule that governs the outcome of each selection. This stage could be further divided into two phases, - an earlier phase where awareness of the rule is implicit, and a later phase where there is an explicit knowledge of the rule that is being tested. After the stage of testing and confirming the rule, the final stage would be the maintenance of the rule over subsequent trials (Bechara, et al., 1997; Crescentini, et al., 2011). Besides the similarities in learning stages, there are also distinguishing components between these two tasks, the Brixton test which is closely similar to the BRFS, assesses rule learning in terms of cognitive flexibility in acquiring and switching of arbitrary rules over few trials, whereas exploratory learning of reward and penalty outcomes occurs over greater number of trials on the IGT and better performance depends on maintaining the learned rule without changing the pattern of selection. Further there is also the difference in the type of feedback given on both tasks which alters selecting behaviour. On the IGT, selection of card decks is motivated by money reward incentives, whereas on the Brixton and BRFS tests, it is visual spatial characteristics that form the feedback of this task. These differences may mean that the BRFS could involve more executive function abilities compared to the IGT, while the IGT recruits more reward-related functions that are emotion-based. Dissociating the behavioural patterns and neural correlates between the two tasks in relation to emotion processes and other cognitive functions in patients with brain injury in the frontal lobe would yield interesting

comparisons to further elucidate the cognitive systems involved since similar frontal lobe damaged patients have been found to be impaired on these tasks (Bechara et al., 1994; Reverberi, Lavaroni, Gigli, Skrap, & Shallice, 2005).

3.1.2 Executive function in rule learning

Studies have reported a possible association of education and executive function related abilities, such as working memory, to both forms of rule-based learning. For non-reward based learning on the Brixton test, a study by van den Berg and colleagues (2009) with healthy older adults and groups of patients with various neurological conditions, found positive correlations between performance on the Brixton test and executive function abilities linked to shifting and memory. In this same study, education was also found to have a positive effect on Brixton test performance (van den Berg et al., 2009). Other studies also found positive associations between rule learning on the Brixton test and performance on a cognitive flexibility task that tests memory and mental calculation abilities (De Frias, Dixon, Strauss, 2009). For studies using the reward based learning - IGT, in healthy older adults, number of years of education was significantly associated with better performance on the IGT (Denburg et al., 2006). Further, a study by Dretsch and Tipple (2008) with healthy participants, found performance on the IGT was linked to executive function abilities such as working memory. Performance on the IGT was significantly impaired by a high working memory load interference task, i.e. digit span. This impairment was specifically during the second stage of learning where possible rules were being tested (i.e. 21st to 80th card selection). This result suggests that cognitive systems involved during the middle learning stages of the IGT are linked to short term memory recall. Another study by Stocco and

colleagues (2009) reported that the learning phase of the IGT was significantly impaired by an interference task. This interference was not observed during the 'blind' trials of the IGT (after rule learning had been achieved when monetary incentives were no longer presented). These findings, contradict previous research which found that a small number of patients with right dorsolateral prefrontal cortex (dlPFC) damage were able to learn on the IGT despite of being impaired on a memory delay task (Bechara, Damasio, Tranel, Anderson, 1998). However, these results were based on a small number of patients (less than 10) and are therefore inconclusive. Further examination of the involvement of executive function abilities and education in rule learning on the IGT and general rule learning in the BRFS are necessary to further understand the similar and differential recruitment of cognitive components in these two learning tasks.

3.1.3 Emotion and apathy in rule learning

Reward-based learning on the IGT has been strongly linked to emotional processes and is potentially also associated with apathy which is a disorder related to emotional processing that influences motivation in everyday behaviour. A dominant hypothesis on the mechanism that mediates learning in the IGT is the somatic marker hypothesis (SMH; Damasio, 1994). The SMH was proposed based on investigations of patients with vmPFC damage who showed impairment in decision-making despite intact executive function abilities. It is hypothesized that these deficits arise from problems in using emotion based feedback before making a choice, i.e. during the period when options were deliberated on. Studies found that patients with vmPFC as well as amygdala damage showed no significant autonomic response change i.e. skin conductance responses (SCRs) for the time period prior

to making a card selection, unlike healthy controls who had significantly higher SCRs prior to disadvantageous card selections which corresponded with more cards selected from advantageous decks on the IGT (Bechara, Damasio, Damasio, & Anderson, 1994; Bechara, Damasio, Tranel, Damasio, 1997; Bechara, Damasio, Damasio, Lee, 1999; Bechara, Tranel, Damasio, 2000). A recent longitudinal study found that patients with vmPFC damage do not learn after several attempts over a six year period, unlike healthy controls who improved in performance every time they performed on the IGT, suggesting that deficits in using emotional feedback for learning on the IGT to be long-term (Waters-Wood et al 2012). Other evidence have also shown that in healthy participants autonomic response, that is SCRs, linked to card selection outcome rather than the time period just before decision-making on card decks was predictive of better performance over the IGT (Suzuki, Hirota, Takasawa, & Shigemasu, 2003). Further evidence of a link between emotion and IGT performance from a study using functional magnetic resonance imaging (fMRI) methods with healthy participants showed significantly increased neural blood oxygenated level dependence (BOLD) signal in the vmPFC during the evaluation of emotive pictures from the International Affective Picture System (IAPS; Lang, Bradley, Cuthbert, 1997) which was positively correlated with performance on the IGT (Northoff et al., 2006). A study on mild depression also found an association between emotion processes and reward based learning. In otherwise normal functioning adults, mildly depressive participants were found to learn better on the IGT compared to non-depressive participants (Smoski, Lynch, Rosenthal, Cheavens, Chapman, & Krishnan, 2008). These findings suggest a strong relationship between emotion based experience and reward based learning.

A different form of abnormal emotional response is observed in apathetic individuals. Apathy defined as an emotion related disorder affecting motivation influencing thoughts, emotional experiences, and actions (Brown & Pluck, 2000; Marin & Wilkosz, 2005). Apathy has also been found to have debilitating effects on reward based learning. A study reported that apathy levels based on the informant ratings scale is associated with poorer performance on the IGT in patients with lesions in the vmPFC and dlPFC (Njomboro, Deb, Humphreys, 2012). In another study, by Fellows and Farah (2005), patients with vmPFC and dlPFC damage were also reported to have significantly higher scores on apathy compared to healthy age-matched controls. The same study also found that apathy scores had significant negative correlation with planning of future events (Fellows and Farah, 2005). This suggest that the ability to predict, reason and make decision based on prior knowledge maybe impaired in individuals who exhibit apathetic symptoms. The current study aims to test in depth the association between emotional processes, apathy and reward based learning for patients with brain injury.

3.1.4 Apathy, general learning, and executive function

Apathy has also been related to executive function abilities. Studies have used the mini mental state (MMSE), verbal fluency, and digit span among various other executive function tests and found significant correlations between apathy scores on various apathy scales and executive function ability in patients (Powell, Al-Adawi, Morgan, 1996; Kraus & Maki 1997; See Review: van Reekum, Stuss, Ostrander, 2005). On the contrary, a study by Njomboro and colleagues (2012) of neurological patients found no significant effects for apathy on performance in the Brixton test. Further investigation to examine the possible

relationship between general learning, executive function abilities and apathy in patients with brain injury would also help in understanding the effect of apathy on different cognitive processes associated with non-reward based learning.

3.1.5 Neuroimaging evidence of differential learning systems

Evidence from neuroimaging studies suggest similar as well as differential brain regions associated with the different types of rule learning on the IGT and Brixton test. In an fMRI study (Crescentini, et al., 2011), using an adapted version of the Brixton test with more rules for learning compared to the original Brixton test, the dlPFC was found to be involved during the learning stage of the Brixton test and the frontal pole was found to be associated with rule learning and testing before explicit knowledge of the rule was learned. However, unlike the Brixton test, the IGT examines rule learning within a decision-making framework that involves reward-based learning within the context of uncertainty and risk (Bechara et al., 1994; Bechara et al 1997). Functional neuroimaging studies have shown the involvement of several brain regions in the performance of the IGT, which included the dlPFC (Ernst et al., 2002; Li et al., 2010), frontal pole (i.e. BA10; Fukui et al., 2005; Lawrence et al., 2009), anterior cingulate (Li et al., 2010; Lawrence et al., 2009), vmPFC (Fukui et al., 2005; Lawrence et al., 2009; Li et al., 2010), and subcortical regions such as the caudate (Ernst et al., 2002; Lawrence et al., 2009). A voxel-based morphometry (VBM) study by Gansler and colleagues (2012) to map healthy grey matter brain regions correlated to learning on the IGT in older adults without brain injury found no significant correlation of grey matter areas and learning using the original behavioural index of performance involving all card decks, i.e. (decks C+D)-(decks A+B), which failed to take into account learning over the IGT, used in the

original study by Bechara and colleagues (1994). However, significant association was found in prefrontal cortex regions, such as the dlPFC, as well as subcortical regions using behavioural indices that included only decks A and D, (i.e. deck A: with frequent wins and losses; and deck D: infrequent and higher losses compared to deck C), which the study claims to decrease the varied cognitive components involved compared to the original behavioural index of IGT performance. The same study also found using the D-A behavioural index, a positive correlation of left ventrolateral prefrontal cortex and right parahippocampal regions for learning during the first half of IGT (i.e. decks 1 to 40). A recent study by Gläscher and colleagues (2012) also using the original IGT and VBM method to ascertain neural correlates of a significant number of patients. The study used total number of safe minus risky card deck selections as a measure of performance which failed to examine overall learning across the entire IGT. The results reported from this study showed the involvement of vmPFC. However, it is not known from this study if patients learned on the IGT since statistical analysis to compare across blocks to ascertain difference in number of safe to risky card deck selections was not carried out. Further, the regression used for the VBM analysis controlled for four cognitive tasks that recruited executive function that were known to involve memory-related abilities and did not add as covariates possible emotional processes involved in IGT performance, which could have resulted in a biased effect showing vmPFC involvement only on the IGT that is well-known to be a reward and emotion related task unlike the other tasks involved. The overall findings suggest that there were similar neural correlates of the dlPFC and frontal pole for both types of rule-learning tasks as well as dissociable neural regions in the prefrontal cortex and other subcortical brain regions that involved in reward-based learning. Further investigation of the similar and differential neural regions involved in reward related learning in the IGT and the non-reward related

learning on the BRFS would enable further understanding of neural regions involved in the different types of rule based learning.

3.1.6 Objectives of current study

This study aims to examine similarities and compare differences using behavioural and function-lesion mapping of an adapted version of the IGT (Lawrence et al., 2009) and the Birmingham rule finding and switching (BRFS) test that is part of the Birmingham Cognitive Screen (BCoS; Humphreys et al., 2012). The main aim of this study is to compare between the two types of clinical measures that assess rule learning: 1) the IGT – involved an emotional component (monetary reward and losses) with one fixed rule, and 2) Birmingham rule finding which does not have an emotional component and involves several rule changes over few trials. Two sets of data were collected from brain-injured patients with varied aetiologies (Table 1). In the first set of data collected, an adapted version of the IGT (Lawrence et al., 2009) was used which consisted of reward or punishment contingencies equivalent to that of the original card decks A and C (Bechara et al., 1994) so as to examine decision-making based on frequent rewards and punishment. A simple picture-categorization task of emotive images from the International Affective Picture System (IAPS; Lang, Bradley, Cuthbert, 1997) was also collected from patients. During testing, patients' galvanic skin response (GSR) as an indicator of physiological-emotional change during learning and categorisation of emotive images was initially collected using Biopac systems, however due to failure to detect a faulty technical setting the GSR data collected could not be further analysed and will not be further mentioned in this report. The second set of data collected from patients was on the BCoS which included a battery of tests

such as the BRFS and other executive function tests which included a questionnaire on self-orientation (personal information, time and location), immediate story recall ability, as well as sustained auditory attention as well as spatial neglect assessment (apple cancellation task). Data from healthy age-matched controls was also collected on the IGT and picture-categorization task, and normative data available on the BCoS tests was also used to compare with data collected from patients. In the analysis, the behavioural index of IGT performance was based on safe minus risky card selections (i.e.[C+D] minus [A+B]) for the early stage of learning (i.e. [2nd block of 20 cards selections] minus [1st block of 20 card selections]), as well as overall learning on the IGT, (i.e. [final block of 20 card selections] minus [first block of 20 card selections]).

This study predicted that brain-injured patients would have lower performance on both learning indices of the IGT (Bechara et al., 1994), as well as lower accuracy scores on the BRFS (Reverberi et al 2005), compared to age-matched healthy controls, due to general cognitive deficits following an injury. Both the earlier stage (block 2 minus block 1) and overall performance (block 5 minus block 1) on the IGT were predicted to positively correlate with accuracy on the BRFS, given the assumed overlap in cognitive processes. Age was not predicted to have a correlation to performance, while education was predicted to have a positive correlation to both types of learning in the patient and age-matched control groups. Learning on the IGT was predicted to correlate with number of pictures categorised as having positively or negatively valence. No correlation was expected between the performance on the BRFS and number of pictures positively/negatively categorised for valence. Performance on the IGT was expected to have a negative correlation with scores on apathy scales, such as the self-rated version (Marin, 1991; AES-self rated) and an adapted

version of the AES, that is the Lille Apathy Rating Scale (Sockeel, Dujardin, Devos, Deneve, Destee, Defebvre, 2006) as well as the informants version of the Apathy Evaluation Scale (Marin, 1991; AES-informant). Similarly, accuracy on the BRFS was expected to correlate with scores on the apathy scales. Learning on the IGT and BRFS were predicted to correlate positively with executive function abilities, namely immediate recall and sustained attention.

MRI brain structural images were obtained for the patient group only to identify the damaged neural regions that are associated with IGT and BRFS performance. The aim was to find grey matter regions that are specifically for reward based learning and general non-reward based learning, controlling for age, education, apathy, emotion processes, and executive function abilities in the regression, which no other study to date has carried out. Less healthy grey matter in the dlPFC and frontal pole (BA 10) was expected to be positively correlated with lower performance on the BRFS (Crescentini et al., 2011). Similarly, lesser normal healthy tissue in the vmPFC (Gläscher et al., 2012) was predicted to positively correlate with lower learning on the IGT (block 2 minus block 1; block 5 minus block 1). A conjunction analysis on neural regions and learning on both tasks was predicted to find a similar brain region in the frontal pole.

3.2 Methods

3.2.1 Participants

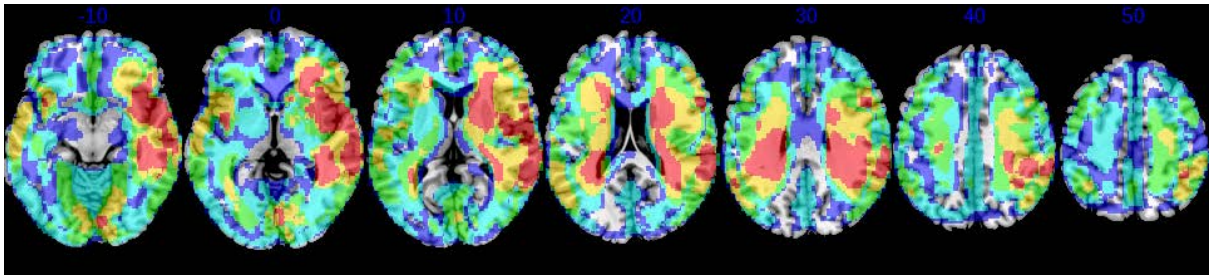
Twenty-four patients (3 females) with brain injury took part in the study. The ages of the patients ranged from 39 to 80 years (mean age 65.4, SD=10.8). The inclusion criteria for the recruitment of participants were that (a) patients had an acquired brain injury and (b) patients were not in the acute stage of brain injury (> 12 months post injury). Patients were excluded if they could not follow the instructions of the IGT as assessed during the practice task. Two patients (aside from the 24 participants who were kept in the study) had to be excluded based on their inability to complete the IGT practice trials. 2 patients' data on the BRFS, apathy scales, and BCoS assessment tools was not available as these patients discontinued their participation in the study for reasons outside of the study. The missing data was replaced by the average of the group. 20 of the patients suffered from stroke, 2 from anoxia, 1 from encephalitis, 1 cortical degeneration (Table 3.1). Figure 3.1 shows the overlap of lesion areas of the patients recruited, as shown the lesions were distributed across the entire cortex, though the most common lesion was to the right frontal parietal lobes (red colour areas)

For comparison, 19 age-matched healthy controls participants were recruited within an age range of 40 to 82 (14 males, 5 females, mean age 65.16, SD=13.0). The data for the older participants (>55yo) of this sample was reported in Chapter 2. Patients and age-matched controls were recruited from a group of volunteers set up by the Behavioural Brain Sciences Group at the School of Psychology, University of Birmingham. Consent to participate was obtained according to ethical protocols at the School of Psychology and Birmingham University Imaging Centre (BUIC).

Table 3.1 Patients' cognitive and demographic profile

Patient	Age	Gender	Handed.	Edu*	Aetio.	IGT B2-1	IGT B5-1	BRFS	Ori-P	Ori-T&S	Sus Attn	Imm Rec	App Can
1	63	Fem	R	2	stroke	-1	-12	4	8	6	8	4	-3
2	78	Mal	R	4	stroke	6	4	15	8	6	-4	0	-3
3	64	Mal	L	3	stroke	10	0	14	7	5	-5	9	15
4	63	Mal	R	5	stroke	10	4	13	8	6	-1	6	0
5	57	Mal	R	2	enceph	1	-1	16	6	3	-2	6	2
6	66	Mal	R	5	stroke	17	19	12	8	5	4	12	2
7	39	Mal	R	5	stroke	-5	1	16	8	6	1	0	0
8	78	Mal	R	2	anoxia	1	-1	2	7	4	3	0	-3
9	67	Mal	R	4	cort. den	8	4	12	8	6	2	9	0
10	62	Mal	R	5	stroke	-5	4	17	8	6	1	4	1
11	78	Mal	L	2	stroke	3	2	1	8	6	1	6	0
12	70	Mal	R	3	stroke	5	9	10	7	5	6	4	-2
13	76	Mal	R	3	stroke	2	2	16	8	6	-1	9	-1
14	72	Mal	R	3	stroke	-3	3	2	8	5	0	6	0
15	40	Fem	R	3	stroke	16	28	9	8	6	1	5	0
16	59	Mal	R	3	anoxia	6	5	4	8	6	0	7	0
17	80	Mal	R	2	stroke	2	7	3	8	6	1	6	-4
18	70	Mal	L	2	stroke	-4	1	0	3	5	1	3	-1
19	77	Mal	R	4	stroke	2	2	6	8	6	0	10	10
20	77	Mal	R	4	stroke	0	-3	12	8	6	-1	6	0
21	79	Mal	R	1	stroke	-2	-4	9	8	6	6	2	0
22	55	Mal	R	2	stroke	4	4	15	8	6	0	4	-1
23	40	Fem	R	3	stroke	2	1	9	8	6	1	5	0
24	52	Mal	R	2	stroke	7	-1	1	0	5	-2	0	0

* Categories of education: Primary school = 1, Secondary school = 2, College = 3, Non-university diploma = 4, University diploma = 5. Acronyms used: Handed.: handedness; Aetio.: aetiology; IGT B2-B1: IGT early learning for block 2 minus block 1; IGT B5-B1: IGT overall learning for block 5 minus block 1; BRFS: Birmingham rule finding and switching test; Orient-P: orientation-personal; Orient –T&S: orientation- time and space; Sus Attn: sustained attention; Imm Rec: immediate recall; App Can: apple cancellation; Encepha: encephalitis Cort.Den.: cortical denegeration.



1 2 3 4 (number of patients with overlapping lesions)

Figure 3.1 Overlap of lesion areas for 24 patients. Red colour regions indicate the highest number of overlapped lesion areas.

3.2.2 Procedure

Each participant took part in five parts of the study: 1) IGT, 2) BRFS, as part of the BCoS neuropsychological assessment tools, 3) emotion categorising task, 4) two apathy scales, 5) MRI scanning. Participants were first given practise trials for all tasks to ensure they understood instructions and could successfully carry out a few trials before beginning testing. Further, apathy data for the informant's version of Marin's (1996) apathy questionnaire was collected from members of the BCoS team who worked on a regular basis with this sample of patients. Data from the BCoS was available for the patients as part of their routine local assessment.

3.2.2.1 IGT, emotional picture categorization task, and apathy scales

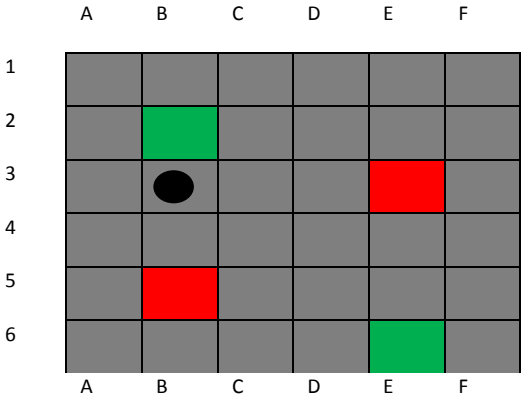
The computerized version of the IGT, picture categorization task, as well as the pen and paper self-rated apathy scales (AES and LARS) used in this study are the same as the previous chapter of this thesis (see: Chapter 2, Methods section).

The informant version of the AES (Marin et al., 1991; Appendix 4) was also used in this study. Questions on the informant version are similar to the self-rated version of the AES, although statements are phrased in the third person narrative (e.g. 'He is interested in learning new things'; 'Getting things started on his own is important to him'; 'Seeing a job through to the end is important to him'). Each statement is rated in the same way as the self-rated version, and responses are also scored similarly. A score of AES that is above or equal to 37 is considered to reflect the presence of an apathetic condition (Marin et al., 1991).

3.2.2.2 Birmingham rule finding and switching (BRFS)

This test was conducted as part of the BCoS assessment. Patients were tested on their ability to find an abstract rule and to learn to switch within and across rule domains. Each stimulus was presented on a grid made up of an array of six columns and six rows (Figure 3.2). Cells were coloured grey except for two cells in red and two cells in green. The aim of the task was to learn to predict the movement of a black circle shape across the grid. The circle shape moves according to a rule, but this rule switches. The switch could be within a domain (e.g. spatial role, move to one-left, move to one-up) and across to another domain (e.g. switch from a spatial rule (move one-up) to a colour rule (move from green to

red). There were 3 rules to learn on the task, and between 4 to 7 trials for each rule, with 19 trials altogether on the task.



Page 1 of stimulus booklet.
Participant instructed to point to a possible square on the grid where the circle will move to next.

Figure 3.2 Example of stimulus of the Birmingham rule finding and switching task.

To begin the task, participants were shown the stimulus and asked to point to the black circle shape, to ensure that a response of pointing to the stimulus could be given. Participants were then told that the circle would move to different locations on the grid from one page to another. The circle shape could move to any position on the grid, and could move from grey to coloured cells. However, they were told to observe carefully where the circle shape moved on each page and they were told that the movement was not random but according to a pattern and that this pattern could change. Participants had to predict the position where the circle shape would move to next. Each trial was presented together with the previous trial for 15 seconds. The location of the circle in each trial could match the rule-base prediction, or when a switch occurred would match a new rule. Correct response was counted as the number of correct rule-base prediction made.

Practice trials where participants were shown where the circle shape moved over 2 trials and were asked to guess where the circle shape would be on the third trial before being given feedback if the prediction was wrong. The task was stopped when there was less than 2 correct responses at the 11th trial.

3.2.2.3 Executive functions tasks

Patients were also assessed for other executive function abilities using BCoS, such as patients' orientation, immediate recall, and sustained attention were examined.

3.2.2.3.1Orientation questions – personal information, time and space

Patients' orientation was assessed by asking questions about awareness of personal information (E.g. what is your first name? what was your occupation?). There were 8 questions asked about their personal information and each question was timed so as not to exceed 15 seconds per question. Scores were the number of correct responses, and the maximum score was 8.

Patients were also asked questions on their knowledge of present time and space (E.g. Where are you right now? What day of the week is it?). There were 6 questions asked and each question was timed so as not to exceed 15 seconds per question. If patients gave an incorrect answer, multiple choices were provided. Scores were the number of correct responses and for instances when multiple choice were provided, these scores were also included. The maximum score was 6.

3.2.2.3.2 Immediate story recall task

Memory was assessed using immediate recall and recognition of a story. Patients were asked to listen to a story that contains 15 units of information (e.g. Mrs Davies/ from Manchester/..) and to recall as many details as possible, once in a free recall (maximum of 2 seconds) and then again in multiple choice trials for details of the story that were not recalled or recalled incorrectly. Scores on this task was the number of correctly recalled or recognised units of information. The maximum score is 15.

3.2.2.3.3.Sustained attention task

Patients were presented with a list of 6 pre-recorded words, nine times each. Three of these words were target words that participants had to respond to by tapping on the table, and the other three words had to be ignored (distracter words). Target words ('no', 'hello', 'please') were closely related to distracter words ('yes', 'goodbye', 'thanks'). Words were chosen for their familiarity in everyday conversations. The words were presented over 3 blocks of 18 words and in a randomised order. Performance measured sustained attention over the 3 blocks. The task was stopped if the participant made more than 8 errors. This task also measured selective attention to target words in inhibiting responses to related distracter words. At the end of the task, participants were asked to recall the 3 target words and distracter words, and this task was also a measure of working memory. The maximum number of correct responses was 18 per block of words. The score used for analysis was the index of sustained attention which was the difference between number of correct responses in block1 and block 3.

3.2.2.3.4 Apple cancellation task

Neglect was measured to ensure that performance was not affected by visual impairments or spatial attention biases. In this task an A4 sheet was shown to the participants in the landscape orientation. This sheet contained line drawings of whole apples and distracter images of apples with either left or right missing part. The patients' task is to cross only the complete apples. Spatial neglect is measured by the different numbers of apples crossed on the left or the right side of the sheet, and by the difference in number of right or left incomplete distracter apples being crossed. Equal number of apple crossed on the left and the right, indicates no neglect (right –left = 0), while more apple crossed on the right than left, indicate left neglect (right –left > 0).

3.2.2.4 Statistical Analysis of the behavioural data

Correlation analysis of age, handedness, education, behavioural performance on the IGT, BRFS, picture categorizing task, scores on the two apathy scales, as well as scores from BCoS, namely, orientation, immediate recall, sustained attention, and apple cancellation was carried out. Results were corrected for multiple comparisons.

3.2.2.5 Voxel-based morphometry (VBM)

Voxel-based morphometry (VBM) was performed with small volume correction using grey matter maps and specific neural regions based on coordinates of peak values reported in previous studies. General linear model statistics was used in this method of analysis to

ascertain correlations between grey matter volume with abnormal tissue and behavioural scores on IGT and BRFS (Ashburner & Friston, 2000). Anatomical scans for each patient were obtained using a 3T Philips Achieva MRI system at the Birmingham University Imaging Centre. An 8-channel phased array SENSE head coil was used with a sense factor of 2 to acquire a sagittal T1-weighted sequence (TE/TR=3.8/8.4ms, voxel size 1x1x1mm).

3.2.2.5.1 Preprocessing of structural scan

Patients' T1 scans were converted into nifti format for analysis using MRICron (Chris Rorden, Georgia Tech, Atlanta, GA, USA). Analysis software SPM8 (Statistical Parametric Mapping, Welcome Department of Cognitive Neurology, London UK) was used for the pre-processing of the data. Brain structural scans were transformed in the standard MNI space with a modification (Seghier et al., 2008) of the unified- segmentation procedure (Ashburner & Friston, 2005). The unified-segmentation procedure uses tissue classification that depends on the signal intensity in each voxel and on a priori knowledge of the expected localization of grey matter (GM), white matter (WM), cerebrospinal fluid (CSF) in the brain. The improved segmentation procedure (Seghier et al., 2008) allowed for better tissue classification and spatial normalization of brain lesion areas by including an added class for the abnormal tissue, i.e. lesion areas, so as to account for the voxels that are in these lesion areas and hence do not reflect grey matter or white matter tissue (Seghier et al., 2008). Successful segmented scans were checked by eye, and then smoothed with a 12mm FWHM Gaussian filter, to account for the assumption of the random field theory that is involved in the statistical analysis (Worsley, 2003).

3.2.2.5.2 VBM analysis

The normalized and smoothed grey matter probability maps were used in the statistical analysis with SPM8 using the general linear model framework. The main aim of this study was to compare between two types of clinical tests that assess different rule learning abilities: 1) the IGT – involved an emotional component (monetary reward and losses) for an earlier rule learning stage and the final rule maintenance stage of the IGT, and 2) Birmingham rule finding which does not have an emotional component and involves rule changes over few trials. In addition the model included the following covariates to control for potential confounding effects: age, education, the negative and positive emotive score from the IAPS emotion categorising task, the scores on the AES and LARS, as well as the scores from BCoS assessment tools such as the orientation, immediate recall, sustained attention, and apple cancellation. The possible covariate of age, handedness and education was also included in the analysis.

A voxel-by-voxel correlation analysis of the whole brain was conducted to test for possible relationships between damaged neural tissues and behavioural scores. Voxel level results were threshold at p-level of 0.005, uncorrected for multiple comparisons, and cluster level analysis was carried out on voxels that survived this threshold, with a cluster size of at least 50 voxels.

Given the a-priori hypothesis it was predicted that reward based learning will involve the vmPFC, anterior cingulate, and caudate. Cluster peak voxel coordinates of the vmPFC, anterior cingulate and caudate reported by Lawrence and colleagues (2009) to define the

regions of interest for this study. Non-reward based rule learning and switching was expected to involve the frontal pole, and cluster peak voxel coordinates of the frontal pole from a previous study on the Brixton test was used (Crescentini, et al., 2011). For the conjunction analysis we predicted a similar neural region of the dlPFC for reward learning in the IGT and general rule learning on the BRFS, using the peak cluster voxel coordinates from the study by Crescentini and colleagues (2011).

3.3 Results

3.3.1 Behavioural performance

The description of the average behavioural data of patients and age-matched controls on the IGT, picture categorising task, and apathy scales presented with demographics of both groups is presented in Table 3.2. The comparison between patients' normalised results for the BRFS and other executive function tasks to normative data on the BCoS is shown in Table 3.3.

Table 3.2 Comparison between patients (n=24) and age-matched controls (n=19) for mean scores on the IGT, picture categorising task, and apathy scales.

	Patients [mean (SD)]	Age-matched controls[mean(SD)]	Statistics t(df=41)value	Confidence level (95%CI)
Age	65.65 (12.75)	65.16 (12.98)	-0.02	-7.72 to 7.57
Education	3.1 (1.18)	3.32 (1.11)	-0.66	-0.94 to 0.48
Gender (M/F)	21/3	14/5		
IGT				
Block 5-1	3.43 (3.78)	5.58 (11.3)	-0.81	-8.16 to 3.5
Block 2-1	3.26 (5.97)	3.26 (7.45)	-0.08	-3.95 to 4.4
Motorcontrol	4.13 (3.27)	8.47 (2.1)	-5.04*	-6.09 to -2.61
IAPS task				
Positive rating	10.67 (5.31)	11.68 (4.16)	-0.68	-4.02 to 2
Negative rating	9.21 (4.4)	6.32 (3.28)	2.38*	0.44 to 5.3
Apathy scales				
AES – self	27.08 (6.05)	26.26 (6.26)	0.67	-3 to 4.63
LARS	-25.58 (7.67)	-29.74 (4.46)	2.1*	0.15 to 8.16

** $p < 0.05$*

Table 3.3 Patients' normalised scores on BRFS, BCoS executive function tasks, and normative data.

Cut off scores based on 5th percentile and smoothed across age groups

	Patients(n=22)	Normative data (n=100) based on age		
		≤64 (n=34)	65 – 74 (n=33)	≥75 (n=33)
BRFS accuracy scores	0.85	<6	<5	<4
Immediate Recall	0.84	6	6	3
Orientation –Personal info.	3.38	8	8	8
Orientation – time & space	3.56	6	6	6
Sustained Attention	0.16	>1	>1	>2
Apple Cancellation	0.06	<-2 or >2	<-2 or >3	<-2 or >1

3.3.1.1 IGT

There was significant difference in advantageous more than disadvantageous card selections over five blocks of the IGT ($F[1,88] = 2.95$; $p < 0.05$), which was nearly along a quadratic pattern across blocks ($F [1,22] = 4.31$; $p = 0.05$). There was no significant difference between patients and age-matched controls in learning performance on the IGT (block 2 minus block 1, $t = -0.08$, $p > 0.001$; block 5 minus block 1, $t = -0.81$, $p > 0.001$) although in the motorcontrol task the patient group was significantly slower than age-matched controls ($t = -5.04$, $p < 0.001$). The results of learning on the IGT, i.e. index of number of safe to risky choices for the earlier stage of rule learning between block 2 and block 1, as well as overall learning between block 5 and 1, show that patients and age-matched controls were able to learn on the task, with the exception of 3 patients and 5 controls who did not show learning on both indices. Figure 3.3 presents the distribution of rule learning during the early phase of the task among patients. Figure 3.4 shows the distribution overall rule learning for patients.

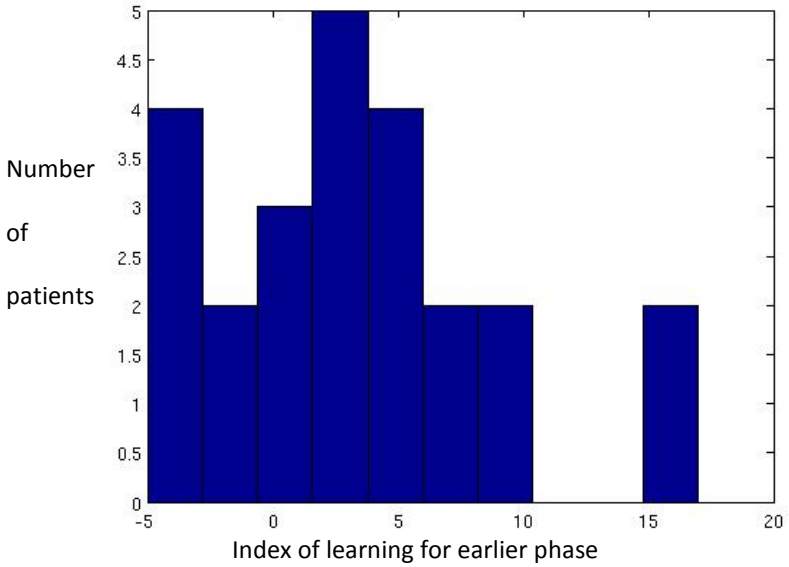


Figure 3.3 Distribution of the number of patients and index of learning during the early stage of the IGT (i.e. block 2 minus block 1).

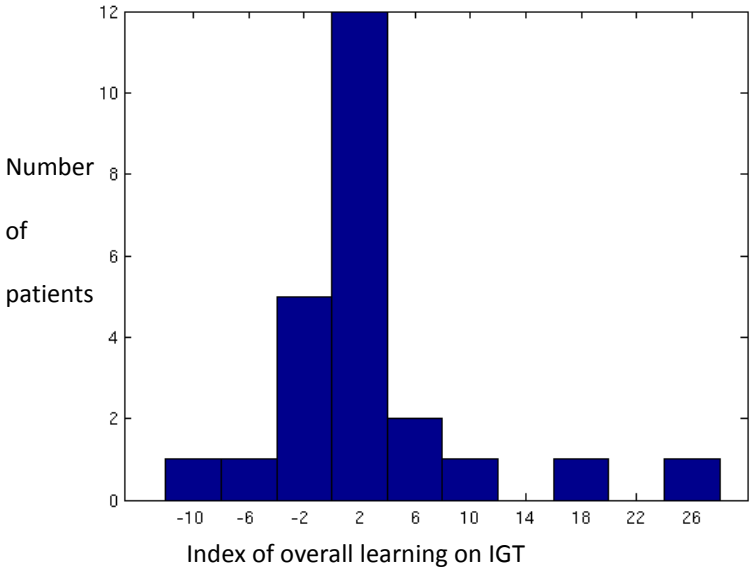


Figure 3.4 Distribution of the number of patients and index of overall learning on the IGT (i.e. block 5 minus block 1)

3.3.1.2 Birmingham frontal rule finding task

Number of correct responses on the BRFS for patients was over a range of 0 to 17 (mean 9.43 ± [SD] 5.28), out of a possible range of scores that was between 0 to 18 (Figure

3.5). Two patients did not have scores for the BRFS for reasons mentioned in the methods participant section.

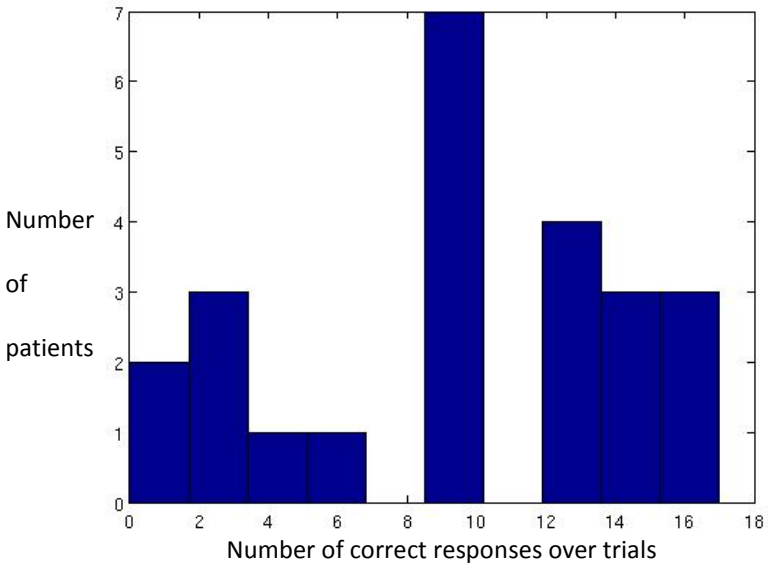


Figure 3.5 Distribution of the number of patients and number of correct responses over trials on the Birmingham rule finding and switching task.

3.3.1.3 Picture categorising task

For the picture categorising task, patients categorised a greater number of pictures as negative compared to healthy control ($t = 2.38$, $p < 0.05$), however the number of images categorised as positive did not differ significantly ($t = -0.06$, $p > 0.05$). Number of times patients categorized the IAPS images as positively valence was between 2 to 23 (mean 10.67 ± [SD] 5.31), from a possible range of 0 to 29. The number of times patients categorized the images as negatively valence was between 3 to 18 (mean 9.21 ± [SD] 4.4), from the possible range of 0 to 29. Number of negatively categorized images (Table 4.) was significantly higher for the patients compared to healthy controls. There was no significant difference between participant groups for number of images categorised as positive or neutral.

3.3.1.4 AES – self rated, AES –informant rated, and LARS

On the apathy scales, for the LARS significant difference was found between the groups ($t = 2.1$, $p < 0.05$), but no difference was found for the AES-self rated ($t = 0.67$, $p > 0.05$). Two patients did not have scores on the apathy scales. Remaining patients' scores on the AES –self rated was between 18 to 39 (mean 26.65 ± [SD] 5.80), out of a possible range of 18 to 72. For the LARS, patients' scores was between -34 to -11 (mean -26.74 ± [SD] 5.28), out of a possible range of -36 to 36. There was a significant positive relationship found between AES and LARS ($r = 0.67$, $p < 0.001$). There was significant difference between patients and healthy controls on the LARS, patients scored higher compared to controls. However, no significant difference was found between both groups on the AES –self rated. On the informant version of the AES, scores was between 18 to 63 (mean 39.24 ± [SD] 14.57).

3.3.1.5 Other BCoS tasks

3.3.1.5.1 Orientation questions

Patients' scores on the personal information orientation questions between 3 to 8 (mean 7.52 ± [SD] 1.11), and for a possible range of 0 to 8. Scores on the orientation questions regarding time and space was between 3 to 6 (mean 5.52 ± [SD] 0.78), for a possible range of 0 to 6. There were 2 patients with no scores on this task and other BCoS tests as mentioned before. The range of questions answered correctly was similar to normative data of healthy age-matched controls.

3.3.1.5.2 Immediate story recall task

Memory and story recognition scores was between 0 to 12 (mean 5.24 ± [SD] 3.15) for patients, for a possible range of score from 0 to 15. These scores were similar to normative data shown in Table 5.

3.3.1.5.3 Sustained attention task

For the index scores on sustained attention, i.e. number of correct responses on block 1 minus block 3, patients' performance ranged from -4 to 8 (mean 0.95 ± [SD] 3.01). Performance on this test was similar to normative data (Table 5).

3.3.1.5.4 Apple cancellation

For asymmetry scores that indicate potential effects of neglect on other task performance, i.e. positive values would indicate neglect on the left visual field, and negative values showing right visual field neglect, the range of patient scores was -4 to 15 (mean 0.52 ± [SD] 4.14). These scores were within the same range as normative data (Table 5).

3.3.2 Correlational Analysis

There was a significant a positive correlation between type of education and scores on the BRFS ($r = 0.57$, $p < 0.05$; Table 3.4). However, type of education was not found to be significantly correlated with IGT performance (block 2 minus block 1, $r = 0.21$, $p > 0.05$; block 5 minus block 1, $r = 0.32$, $p > 0.05$). There was a significant positive correlation between overall learning on the IGT (i.e. block 5 minus block 1) and number of images categorised as negative ($r = 0.56$, $p < 0.05$), however there was no significant association between earlier phase rule learning (i.e. block 2 minus block 1) and number of negatively categorised images ($r = 0.29$, $p > 0.05$). There was no correlation found for IGT performance and number of positively categorised pictures (block 2 minus block 1: $r = -0.16$, $p > 0.05$; block 5 minus block 1: $r = -0.13$, $p > 0.05$). In contrast, BRFS accuracy scores was not correlated with negative or positive categorisation of pictures (negative, $r = -0.26$, $p >0.05$; positive, $r = 0.02$, $p > 0.05$). Reward based rule learning on the IGT (block 2 minus 1; Table 3.5) was predicted by performance on the immediate recall of a story ($r = 0.53$, $p <0.05$). There were no other reliable correlations. Specifically early and overall learning on the IGT and learning on the BRFS were not reliably associated with the scores on the AES-self rated, AES-informant rated, LARS, with the BCoS measures of sustained attention, spatial neglect and orientation.

Table 3.4 Patients' data; Relationships between IGT, BRFS, and performance on emotion related abilities, such as IAPS picture task, Apathy scales (Pearson correlation coefficients; n=24)

	Age	Education	IGT B2-B1	IGT B5-B1	BRFS	IAPS –Pos	IAPS-Neg	AES-Inf	AES-Self	LARS
Age	1.0	-0.18	-0.19	-0.26	-0.34	0.18	-0.01	0.74	0.03	0.01
Education		1.0	0.21	0.32	0.57	-0.06	0.09	-0.44	-0.17	-0.28
IGT B2-B1			1.0	0.68**	0.23	-0.16	0.29	-0.27	-0.1	0.24
IGT B5-B1				1.0	0.16	-0.13	0.56*	-0.25	-0.01	0.09
BRFS					1.0	-0.26	0.02	-0.38	-0.25	-0.22
IAPS-Pos						1.0	-0.22	0.2	-0.18	-0.24
IAPS-Neg							1.0	-0.14	-0.1	-0.21
AES –Inf								1.0	0.34	0.3
AES – self									1.0	0.67**

*p <0.05; ** p <0.001

Table 3.5 Patients' data; Relationships between IGT, BRFS, BCos executive function tests (Pearson correlation coefficients; n=24)

	Education	IGT B2-B1	IGT B5-B1	BRFS	Orien-P	Orien-T & S	Imm Rec	Sus Attn
Age	-0.18	-0.26	-0.19	-0.34	0.23	0.54	0.86	0.03
Education	1.0	0.32	0.21	0.57*	0.32	0.27	0.24	-0.25
IGT B2-B1		1.0	0.68	0.23	0.19	-0.03	0.53*	-0.13
IGT B5-B1			1.0	0.16	0.06	-0.02	0.29	-0.06
BRFS				1.0	0.38	0.26	0.1	-0.34
Orien-P					1.0	0.54*	0.21	0.05
Orien-T & S						1.0	0.06	0.7
Immed Recall							1.0	-0.14

*p <0.05

3.3.3 VBM analysis

VBM analysis (Table 3.6) found that less healthy grey matter in the caudate impairs the ability to learn during the early stages of the IGT (i.e. block2 minus block1, red blob in Figure 9). The cluster survived family wise small volume correction using the coordinates of the caudate from a previous study (MNI: 6, 21, 0, sphere: 9mm; Lawrence et al., 2009). In contrast, less normal tissue in the left frontal pole (BA10) impaired patient's ability to learn a rule and to switch between rules on the BRFS (yellow blob, Figure 3.6). The cluster survived family wise small volume correction based on coordinates of the left frontal pole from another previous study (MNI: -10, 52, 10, sphere: 15mm; Crescentini et al., 2011). However, the correlation between less healthy grey matter in right frontal pole and BRFS

performance was found only for uncorrected analysis of $p < 0.001$, thresholded at 50 voxels. In the analysis to ascertain similar as well as dissociated brain regions involved in reward based rule learning on the IGT and accuracy on the BRFS, the conjunction analysis showed that less healthy tissue in left frontal pole (MNI: -10, 52, 10, sphere: 15mm; Crescentini et al., 2011) impaired performances on both tasks (Figure 3.6).

Table 3.6 Correlations between grey matter, IGT reward based rule learning and BRFS accuracy scores.

Contrast*	Brain region	Cluster size	X Y Z	t-value
Block 2-1	Right Caudate	427(voxels)	12, 22, 10	3.61
BRFS	Left Frontal pole	523	-20, 56, 6	3.70
Conj. Analysis:				
B2-1 &BRFS	Left Frontal pole	519	-18, 56, 10	3.26

** Contrasts are controlled for age, education, apathy scores on AES & LARS, picture categorising task, BCoS executive function abilities (i.e. orientation, immediate recall, sustained attention).*

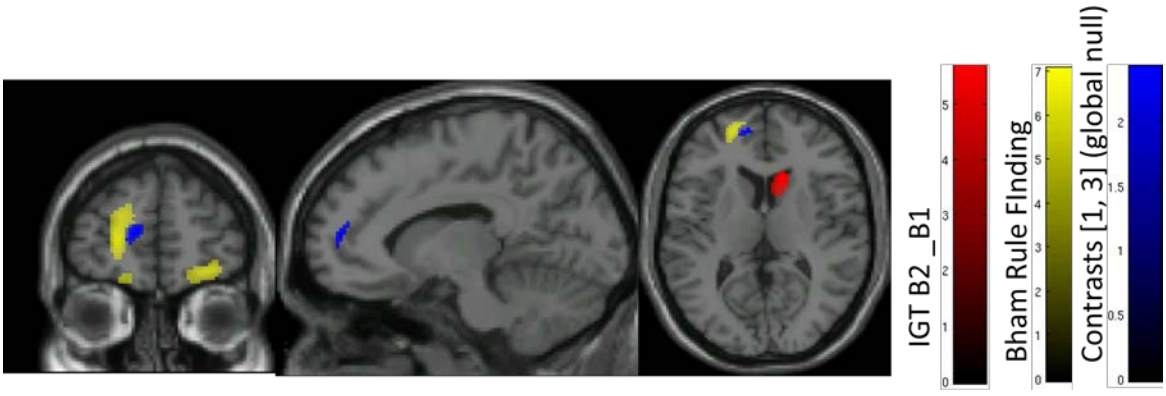


Figure 3.6 Correlation of the region of the right caudate in the performance on the IGT measured by difference in the score,(C+D)-(A+B),between Block 2 and Block1. Correlation of the area of bilateral frontal pole (BA10) with performance on the BRFS. Conjunction analysis of neural regions correlated in both tasks found in the left frontal pole.

3.4 Discussion

The current study showed that patients with neurological conditions have intact reward-based learning ability, although for patients overall learning on the IGT was along a quadratic trend unlike the healthy age-matched controls (reported in chapter 2) who showed a linear pattern of learning on the IGT. For both overall and early learning indices (i.e. block 2 minus block 1 & block 5 minus block 1), patients' performance was similar to age-matched controls who also learnt on the IGT. This was unexpected as patients with brain injury were predicted to have lower performance on the IGT compared to age-matched controls. However, this finding is similar to previous evidence that showed a subset of patients with prefrontal cortex lesions to be unimpaired on learning in the IGT (Bechara et al., 1998). Significantly higher number of pictures were classified as negative in valence by patients compare to age-matched controls. Similarly, patients had significantly higher apathy scale scores on the LARS compared to healthy controls. These findings suggest that patient and healthy age-matched controls may process emotions differently and that the apathetic behaviour may be more common in patient groups than healthy controls.

Patients' overall performance on the IGT had a significant positive correlation with number of images classified as negatively valence on the picture-emotion categorization task. A mild positive association was found between early reward-based learning and classification of negative valence pictures. For age-matched controls (in chapter 2), mild positive association between early learning and classification of positive and negative images was found, although non-significant negative associations were found between overall reward learning and categorization of positive and negative valence images. This

finding suggests that like healthy age-matched controls, emotion maybe linked to shifting away from disadvantageous card selections to perform optimally towards the end of the IGT for brain-injured patients. This supports previous findings that suggest emotion related processes to be involved in learning on the IGT (Bechara et al., 1996; Bechara et al., 1997; Suzuki et al., 2003). Further, this is similar to a study with healthy participants that showed later stage of learning on the IGT was positively associated with evaluation of emotive images (Northoff et al 2006). The significant association between emotion processes in the categorising of negative emotive pictures and IGT performance further points to an interesting link between a possible avoidance strategy and reward related learning in patients with brain injury who learned on the IGT.

No significant association was found for apathy scale scores on the informant's version of the AES, self-rated scales of AES, and LARS, to learning performance on the IGT. This is unlike a previous study by Njomboro and colleagues (2012) which found an association between scores on the informant's version of the AES and IGT performance. The condition of apathy based on self-rated scales, was not found to be present in most patients in this study. Apathy scores on the LARS were significantly higher for patients compared to age-matched controls, which supports previous findings that reported higher apathy scores in patient groups compared to healthy age-matched controls (Fellows and Farah, 2005). The lack of a significant association between apathy for informant's version of the AES and learning performance on the IGT, unlike a previous study (Njomboro et al., 2012) suggests that apathy measured by the AES- informants rated version, does not consistently predict learning behaviour on the IGT for patients with brain injury. The average scores on the self-rated AES and LARS were found to be positively correlated, however no correlation was

found for the Informant version of the AES with either of the two self-rated apathy scales. This finding shows an inter-scale reliability between two self-rated apathy scales, the AES and the LARS, but not the Informant-AES, which is unlike previous findings which reported an inter-rater reliability between the self and informant rated versions of the AES (Marin et al., 1991). A possible reason for this discrepancy was the type of informants used in this study who worked with the patients recruited, unlike informants used in previous study who were close relations of patients (Marin et al., 1991). Future studies should include a clinician's assessment of apathy, using the clinician's version of the AES and also to include the informant's version of the AES that is based on feedback from close relations of patients on the apathy scale ratings.

General rule learning on the BRFS was also unimpaired for brain-injured patients and no significant difference was found between patients and age-matched controls. Performance on the BRFS was found to be mildly associated with overall performance on the IGT, although this was not above significance level. Patient's early learning on the IGT was found to be significantly positively correlated to scores on immediate story recall. This suggests a link between executive function abilities, namely short term memory processes and the earlier stage of learning on the IGT where testing of rules occur. The association found between reward-based learning on the IGT and a type of executive function ability supports previous findings with healthy participants which showed that a high memory load distracter task competes with processes recruited for learning in the IGT (Dretsch & Tipple, 2008). The results also show that reward based learning in the earlier stage of the IGT involve executive function abilities such as immediate recall. The lack of association between reward learning on the IGT and non-reward learning on the BRFS also further

suggests that dissociable cognitive processes are recruited for these two types of rule learning.

Non- reward based learning on the BRFS was found to have a significant positive correlation with type of education, suggesting that rule learning in the BRFS to be positively influenced by academic education. This finding supports previous research which reported a positive correlation between education and performance on a similar non-reward related learning task the Brixton test in healthy older participants (van den Berg et al., 2009). However, performance on the BRFS was not significantly correlated to executive function assessment tests, such as immediate recall and sustained attention. This finding is unlike previous research which showed positive association between non-reward related learning on the Brixton test and executive function abilities related to memory and mental arithmetic (De Frias, et al., 2009). Further, in the current study no correlation was found between apathy scale scores and non-reward based learning on the BRFS which was similar to the findings in a previous study based on the informant's version of the AES and Brixton test performance (Njomboro et al., 2012). Taken together the current study showed that non-reward related rule learning such as the BRFS, unlike on the IGT, is consistently found to be associated with education. These findings also showed that general rule learning on the BRFS is not linked to executive functions abilities such as immediate recall, unlike the IGT, and further suggests differential involvement of cognitive components in non-reward based learning from reward related learning.

The aim of the VBM analysis was to identify dissociable and similar neural regions after controlling for age, education and the same executive function and emotion related processes, which were possible cognitive processes that could influence performance on the

IGT and BRFS. Mapping of correlated abnormal grey matter areas and performance on reward based and non-reward based rule learning task successfully revealed similar as well as differential neural regions to be involved, unlike previous study (Gläscher et al., 2012). Loss of grey matter tissue in the right caudate was identified as significantly positively correlated with early stages of reward learning on the IGT performance (i.e. block 2 minus block 1). This finding supports previous studies which found subcortical regions such as the caudate to be associated with learning performance on the IGT (Ernst et al., 2002, Lawrence et al., 2009). However, unlike previous studies, this finding does not show other previously reported neural regions linked to IGT performance, such as the dlPFC, vmPFC, insula, and the amygdala (Ernst et al., 2002; Lawrence et al., 2009; Gansler et al., 2012; Gläscher et al., 2012) a possible reason could be the close association of these neural regions with executive function abilities and emotional processes that this study controlled for in the general linear model of the VBM analysis. No other known study has identified the neural region specifically associated with improvement over blocks on the IGT. The study by Gläscher and colleagues (2012) used the total number of risky minus safe card selections as the performance measure in the mapping of brain regions correlated with behavioural scores on the IGT which does not take into account learning over the IGT, and further no account was given of the difference across blocks for number of safe more than risky card deck selections on the IGT to indicate if patients learned overall on the task. The previous VBM study also did not control for emotion related processes and included only cognitive tasks in the regression analysis that related to memory type executive function abilities that recruit dlPFC, unlike the current study which kept as covariates in the analysis tests that assesses immediate recall, sustained attention, number of positively and negatively grouped

images from the picture categorization task and apathy scale scores, since these were possible cognitive components which were predicted to affect reward related learning.

The neural region of the left frontal pole was found to be correlated with non-reward related learning on the BRFS, and the medial part of this cluster was found to also correlate in the conjunction analysis of both learning on the BRSF and the IGT. This finding suggests that the left frontal pole is involved in evaluative cognitive processes in rule learning for both reward based and non-reward related rule learning, which supports previous studies involving both types of learning (Crescentini et al., 2011; Lawrence et al., 2009). The dlPFC was not found in this analysis of grey matter correlates and accuracy on the BRSF since the current study controlled for executive function abilities associated with this brain region such as the immediate recall and sustained attention which were predicted to be related. These findings suggest that the right caudate is associated with reward based learning and that the left frontal pole is linked to both learning abilities showing that this neural region is involved in a shared cognitive component in both tasks.

There are several limitations in the study. The investigation of emotion processes was limited in terms of the lack of a measure of emotional arousal. Further, findings in this study was based on grey matter correlates on a regression equation using behavioural performance as covariates, which could differ from findings from fMRI studies which used contrasts of BOLD signal changes between conditions of an experiment. The lack of significant correlation between IGT and BRFS performance scores despite the overlap of the neural region in the left frontal pole in the VBM analysis could be due to the lack of variability in behavioural scores and the small number of patients in this study.

Chapter 4

fMRI investigation of reward-based learning on the IGT

and the relationship with emotional processes.

4.1 Introduction

Several studies have investigated the neural regions involved in learning on the Iowa gambling task (IGT). Previous functional magnetic resonance imaging (fMRI) studies found several key neural regions to be linked to decision-making on the IGT, such as the orbital frontal cortex (OFC), frontal pole, anterior cingulate, amygdala and caudate (Christakou, Brammer, Giampietro, & Rubia, 2009; Fukui, Murai, Fukuyama, Hayashi, & Hanakawa, 2005; Lawrence, Jollant, O'Daly, Zelaya, & Phillips, 2009; Li, Lu, D'Argembeau, Ng, & Bechara, 2010). These neural regions form part of a complex network involved in decision-making on the IGT, however the specific role of each region is still unclear. Particularly, recent studies have examined the role of selection outcome (Christakou et al., 2009), as well as emotional processes related to valence (Northoff et al., 2006) in advantageous card selection as well as the neural regions involved in these different aspects of reward related decision-making on the IGT. This study aims to examine overall and early learning on the IGT in terms of neural regions involved, based on choice outcomes (i.e. rewards or losses), as well as the relationship with the degree by which an individual tend to activate emotional associative region when faced with emotional stimuli (i.e.positive or negative).

Functional neuroimaging studies have found various neural regions associated with decision-making on card decks. The study by Ernst and colleagues (2002) using positron emission tomography (PET), found that decision-making trials compared control trials involved the OFC and the anterior cingulate. These neural regions are similar to the ventromedial prefrontal cortex (vmPFC) that have been associated with decision-making on the IGT in neuropsychological studies (Bechara, Tranel, Damasio, Damasio, 1996; Bechara, Damasio, Tranel, Damasio, 1997; Bechara, Damasio, Damasio, Lee, 1999; Bechara, Tranel,

Damasio, 2000). Another study using fMRI, found significantly higher BOLD response for disadvantageous compared to advantageous selection trials in the medial prefrontal cortex, which was also found to be positively correlated with net number of advantageous more than disadvantegous card selections (Fukui et al., 2005). In an fMRI adapted version of the IGT using card decks with either rewards or punishments presented on each trial, with reward/losses contingencies of decks A and C of the original IGT (i.e. frequent rewards and losses; Bechara, Damasio, Damasio, & Anderson, 1994), significantly higher BOLD signal in the medial frontal gyrus, lateral OFC, posterior frontal gyrus was reported for the whole brain analysis of disadvantageous compared to advantageous card selections correlated with total number of advantageous minus disadvantageous card selections on the task (Lawrence et al., 2009). Further, another study using both fMRI and IGT, found that neural response during selection of advantageous compared to disadvantageous decks was significantly higher in the prefrontal cortex, thalamus, amygdala, and cerebellum which were also positively associated with selecting more from advantageous decks (Christakou et al., 2009). These findings suggest that the OFC and anterior cingulate are involved in decision-making on the IGT and more specifically, medial and lateral prefrontal cortex regions and subcortical regions such as the amygdala are associated with choosing more from advantageous decks.

Studies have also examined the effects of outcome of card selections on selecting more advantageously over the IGT as well as the neural regions involved in processing emotion valence of selection outcomes (i.e. positive rewards or negative losses) that are associated with choosing more advantageous card decks on the IGT. A study found that healthy participants' skin conductance response (SCRs) which measures emotion related

physiological feedback was higher after disadvantageous card selections, and higher SCRs was also associated with learning on the IGT, i.e. gradual increase in selection of from advantageous compared to disadvantageous card decks over the whole task (Suzuki, Hirota, Takasawa, & Shigemasu, 2003). This finding suggests that outcome of card selections has more influence on subsequent card selections than previously claimed. This challenges the somatic marker hypothesis (SMH; Damasio, 1994) which suggests SCRs prior to card selections is due to pre-selection processes where emotion outcome from the card deck about to be selected is re-experienced from previous trials that determines if the card deck would be avoided or chosen from in future trials (Bechara et al., 1996; Bechara et al., 1997; Bechara, et al., 1999; Bechara et al., 2000). An fMRI study on the IGT, examined neural activity for outcome of card selections when money incentive is won or loss showed significant involvement of the ventral prefrontal cortex in processing outcome of card decks for the consistent rewards and penalties on the adapted version of the IGT (Windmann Kirsch, Meir, Stark, Walter, Gunturkun et al., 2006). Further, the study by Christakou and colleagues (2009) also carried out an interesting comparisons between money winning or losing trials that was based on whether the card selection was from advantageous or disadvantageous decks, and found significantly higher neural response in the medial and lateral OFC for the interaction of BOLD contrasts for negative losing more than winning outcomes and the BOLD signal comparison of disadvantageous more than advantageous. Further, a study based on an fMRI paradigm and regions-of-interest analysis that factored in amount of monetary incentive and difference between anticipated reward and real gain, found significantly higher levels of BOLD response in the OFC, insula, striatum and anterior/posterior cingulate for decision-making trials compared to control trials (Li et al., 2010). These findings suggest that emotion feedback of card selection outcome influences

decision-making on the IGT, and neural regions such as the OFC and subcortical regions such as the caudate are associated with reward-related processes for card selections on the IGT.

Emotional processing of visual stimuli (i.e. positive or negative) has also been examined using functional neuroimaging methods, and several emotion-related brain regions have been associated with selecting advantageous card decks on the IGT. In the study by Britton and colleagues (2006), significantly higher BOLD signal was found in bilateral amygdala regions as well as the OFC specifically in the vmPFC for passive viewing of emotive images compared to fixation. Other studies have also found the involvement of the amygdala in processing emotive stimuli (Anders, Lotze, Erb, Grodd, Birbaumer, 2004; Berntson, Bechara, Damasio, Tranel, Cacioppo, 2007). A study also found the vmPFC to be involved in the categorization of emotive images that had positive or negative valence compared to fixation, and the same brain region was also significantly correlated to total number of advantageous compared to disadvantageous card selections (Northoff et al., 2006). However, the use of net score of advantageous minus disadvantageous card decks selection as a measure of IGT performance has limitations in giving an overall measure of learning that shows improvement over trials (Dunn, Dalgleish, Lawrence, 2006). Comparisons between final and initial stages of the IGT would be a better measure of overall performance and correlation with neural activity for emotional processing would provide a better indication of neural regions involved reward-related processing that is also associated with learning over the whole IGT. Further, by comparing number of advantageous more than disadvantageous card selections in the second block of 20 trials to the first block of trials would indicate early learning in the first half of the IGT, and correlation with neural response to emotion valence would enable further investigation of

reward-related processes involved in learning to select advantageously on the IGT that takes place early on in the task.

This study aims to examine neural correlates in healthy young adults that are associated with learning on a version of the IGT that was adapted for fMRI investigation (Lawrence et al., 2009), as well as the relationship between learning on the IGT and neural regions involved in emotional processing, i.e. categorization of emotive images from the International Affective Picture System (IAPS; Lang, Bradley, Cuthbert, 1997). The main focus of this study is to ascertain the neural regions involved in: 1.) learning to select more from advantageous (referred to as 'safe') card decks compared to disadvantageous (referred to as 'risky') card decks overall on IGT (i.e. final block minus first block), as well as early learning in the first half of the IGT (i.e. second block minus first block), including as parameters: outcome of card decks (win or lose), and the outcome of one trial before (win or lose); as well as 2.) neural response in emotional associated regions (amygdala) and its association with overall (block 4 minus block 1) and early (block 2 minus block 1) learning performance on the IGT. This study predicted that healthy young participants would learn overall on the IGT. In the last block of 20 selections compared to first block of 20 cards more safe than risky card deck would be selected. Similarly in the first half of the IGT early learning was also expected with more safe than risky card decks be selected for second block of 20 trials compared to first block of 20 trials. Secondly this study predicted neural involvement in learning to selection advantageously in regions previously linked decision-making and reward-related processes in the IGT. Several predictions were made:

1.) Decision-making compared to motorcontrol trials, may involve neural regions in the vmPFC, extending into the caudate (Lawrence et al., 2009). Linear modulation of BOLD

response in these neural regions that indicate significantly higher involvement (i.e. positive linear change) or significantly lower association (i.e. negative linear change) across blocks on the IGT was explored.

2a.) Type of card deck selected (i.e. safe more than risky decks) and increase over time overall on the task (i.e. interaction of time and cards selected). The correlation to learning performance may be associated with medial frontal gyrus, frontal pole, dlPFC, anterior cingulate, amygdala, insula, thalamus, caudate, and cerebellum. For the interaction of card deck type (i.e. safe more than risky decks) and increase over the first half of the IGT (i.e. positive linear change for block 1 to 2), correlated with learning over the first half of the task (i.e. block 2 minus 1) may involve similar neural regions.

2b.) Type of card deck selected (i.e. risky more than safe decks) and increase/decrease over the IGT (i.e. positive/negative linear change across all blocks), correlated with overall learning was also explored. Type of card deck selected (i.e. safe more than risky decks) and increase/decrease over the first half of the IGT (i.e. positive/negative linear change across blocks 1 and 2), correlated with early learning was also examined.

3.) Response modulation of outcome for one card before, positively/negatively regressed over blocks of the IGT may involve the amygdala and orbital frontal cortex. This prediction was made so as to examine the effects of card selections one trial before, since the SMH has claimed that patients with lesions in the vmPFC, which is an area situated medially on the OFC, and the amygdala have lowered SCRs due to impaired ability to recruit emotion feedback prior to decision-making on card decks (Bechara, et al., 1997; Bechara, et al., 1999). Finding an involvement of OFC and amygdala for this comparison would suggest that heightened SCRs in healthy individuals prior to card selection was not a result of pre-

selection processes before decision-making but of emotion valence related processes of decision outcomes one trial before. This would support previous findings that the correlation between SCRs and increasing number of safe compared to risky card selections over the whole IGT which would be indicative of the effect of outcome from the immediate preceding card selection on the subsequent choice made (Suzuki et al., 2003).

Thirdly this study also predicted that emotional categorization of emotive images for valence (i.e. positive or negative) would involve neural regions previously reported in a similar study which also examined emotional categorization for valence of pictures from the IAPS (Northoff et al., 2006), which may also be associated with overall and early learning on the IGT. Further predictions were made:

1.) Positive compared to neutral images as well as negative compared to neutral images may be associated with neural regions such as the vmPFC, amygdala, and occipital cortex. Similar neural regions may also be positively correlated with learning on the IGT for overall performance (i.e. block 4 minus block 1), as well as early learning on the IGT (i.e. block 2 minus block 1).

2.) Overlap of positive and negative compared to neutral images neural areas that are associated with learning on the IGT was also carried out to examine similarities and differences in neural involvement using conjunction analysis function in SPM 8.

4.2 Methods

4.2.1 Participants

19 volunteers (average age = 23.3years) were recruited. Number of years of education was an average of 15.3 years. No history of neurological or psychiatric problems was reported by anyone recruited for this study. Most of the participants were naïve to the task however 2 participants recruited had previous experience playing the IGT. Nevertheless, they were kept in the study but told that they had to relearn the rules. Participants were recruited through advertisements at the University of Birmingham. The Birmingham University Imaging Centre Ethics Committee approved the study protocol and all participants gave their consent to participate in the study and were paid £20, with the knowledge that payment received was not dependent on their performance on the tasks.

4.2.2 Procedure

4.2.2.1 IGT

Participants performed the version of the IGT adapted for use in fMRI experiments by Lawrence and colleagues (2009; see modifications in Chapter 2, Methods section) where 'risky' card decks with high initial monetary rewards but even higher monetary losses have to be forgone for 'safe' card decks with lower immediate monetary returns but even lower losses that result in overall gains on the task. During the study, participants had to choose 82 cards from 4 separate decks, labelled A B C D. Participants are told that when they select from a card deck they will win or lose money and that the aim of the game was to win increase their profit from a starting amount of £2000. The gains and losses were shown

after each card selection and a green bar at the bottom of the screen gave an indication of the gain or a loss. Card decks A and B were 'risky' giving overall losses on the game if selected from more frequently, while card decks C and D were 'safe', with overall gains if chosen more often from during the task. On the risky card decks, there were large winnings (£190, £200, and £210) or large losses (£240, £250, £260), whereas on the safe card decks, less winnings were given (£90, £100, £110) or less losses (£40, £50, £60).

Each trial lasted between 10-12 seconds. At the start of every trial, the instructions to "Wait" would be presented for 2 seconds before participants are asked to "Pick a card", followed immediately by the reinforcement outcome (i.e. win or lose money) for 2 seconds. Participants had 3 seconds to make a card selection. Between trials interval was 5- 7 seconds, during which a fixation cross was displayed. The duration of the display of the fixation cross was adjusted according to the participants' reaction time, so as that each run of the IGT lasted for 754.91 seconds (12.58 min; Figure 1). 28 motor-control trials were also used during a run of the IGT, where participants were instructed to pick from a specified card from 4 decks displayed, labelled E, F, G, or H, by pressing one of four buttons that corresponds to the position of the card across the screen. The control trial began with the instruction "Pick card E" instead of "Pick a card", and participants were encouraged to respond accurately within 3 seconds and that the correct response would be recorded. After a response, participants would be given the feedback that "You picked a card" for a duration of 2 seconds. The green bar at the bottom of the screen did not increase or decrease during these trials. The colour of the decks E, F, G, H was different from decks A, B, C, D. Other appearance and structure of trials of the control task was the same as trials of the

experiment task. These trials were presented in blocks during the same run as actual card selection trials, from trials 1-10, 31 - 38, and 60-69. 2 runs of the IGT was carried out, with 260 scans were collected for each run of the IGT. For each participant, there were 82 decision making trials and 56 motor-control trials in total.

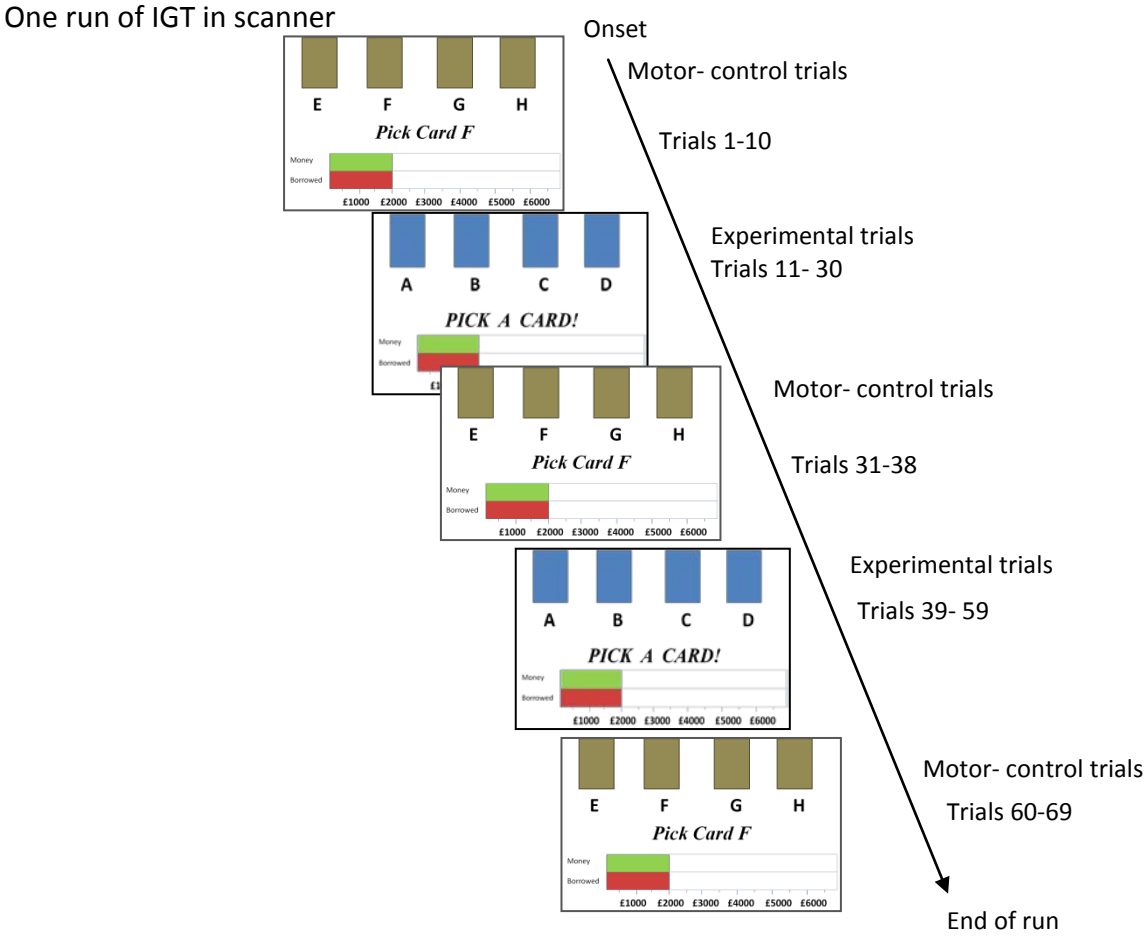


Figure 4.1 Example of one run and timeline of a card selection trial of the IGT.

Participants were given instructions (Appendix 1) and 6 practice trials on a desk and computer before going into the scanner. The 6 practice trials consisted of 2 trials of the control task followed by 4 trials from the experiment task. The practice trials were to familiarise participants of the appearance and layout of the response buttons of the task. After instructions and practice trials were administered, participants proceeded into the scanner and a right-handed button box was used as all participants recruited were right-handed the layout of the 4 button keys of the button box corresponded with the positions of the 4 card decks on the screen.

4.2.2.2 Picture-categorization task (emotion localiser task)

Participants viewed a series of pre-rated emotional images from the International Affective Picture System (Lang, et al., 1997) as part of a picture-categorization task while being scanned. The task was presented on E-prime version 1.1. Each run included 90 images (note that more pictures were used in the current fMRI study than the same task from the previous chapters). 30 negative images (mean valence rating: 2.91; SD: ±0.94), 30 positive images (mean valence rating: 7.56; SD: ±0.5), and neutral images (mean valence rating: 5.73; SD: ±0.84). Each image was displayed for 3 seconds. Before the onset of each block of positive, negative or neutral images, a fixation cross was presented for 3 seconds in the middle of the screen. There was a 15 seconds resting period between blocks of images to ensure that BOLD signal levels were at resting state levels at the beginning of a next block of pictures. One run of the task in the scanner consisted of 9 blocks of 10 pictures, and 3 blocks

of each emotion category of positive, negative, or neutral images presented in counterbalanced order over the task which lasted for 429 seconds (7.15 min; Figure 4.2). Participants categorized these pictures as 'positive', 'negative' or 'neutral' using the right hand button box whilst in the scanner. Participants instructed and also reminded at the beginning of each run that 'you have 3 seconds to respond to what is on the screen. Your task is to click a button in response to how the image makes you feel: click the left button if the picture makes you feel positive, the middle button if the picture is neutral, and the right button if the picture makes you feel negative'. However, these behavioural responses were not recorded as this task was treated only as a localiser task for brain regions involved in 'raw' emotion related processes. 2 runs of the picture categorization task were carried out. On each run of the picture-categorization task, 143 scans were obtained.

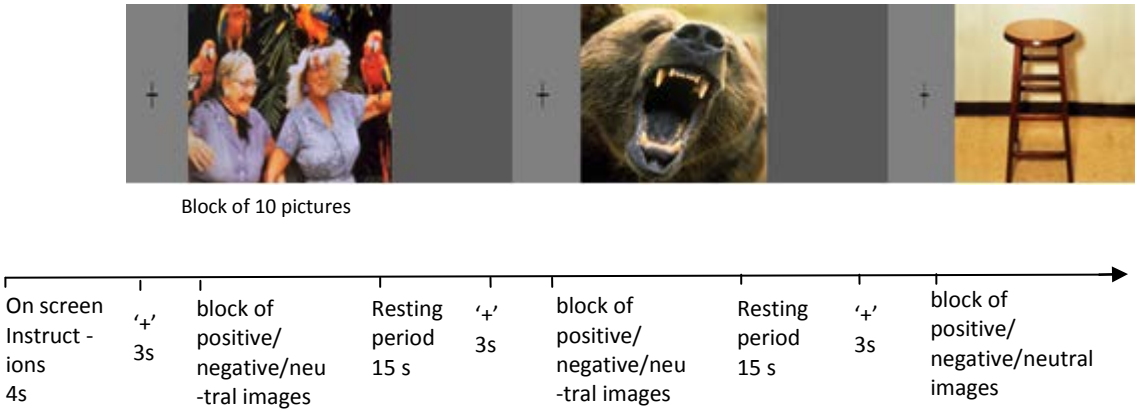


Figure 4.2 Picture categorization task: 3 seconds fixation cross before each block of 10 images from positive, negative, and neutral categories interleaved by 15 seconds resting time.

4.2.2.3 fMRI Image acquisition

Gradient echo echoplanar imaging (EPI) data was collected on a Philips Achieva system 3 Tesla MRI magnet at the Birmingham University Imaging Centre (BUIC). T2-weighted whole brain volumes of 2.5mm thickness, in sagital view, TE= 35 ms, TR= 3s, flip angle of 85˚, field of view 240 cm, 2.5 × 2.5 × 2.5 mm voxel matrix, was acquired using Phillips Sense coil, P reduction (AP) 2. Stimuli were presented onto a screen in the scanner projected on a mirror fixed on the head coil. High resolution T1 structural data was also collected for normalization and coregistration.

4.2.2.4 fMRI analysis

Whole brain analysis was carried out using MATLAB 7.9 (The Mathworks Inc., 2009) and SPM 8 (Wellcome Trust Center for Neuroimaging, 2009). For preprocessing, EPI volumes for both IGT and picture-categorization task were spatially realigned to correct for head movements and unwarped to correct for movements by distortion interactions (Ashburner and Friston, 2003). The structural T1 was then co-registered to the EPI. DARTEL algorithm was to create a groups' average brain template. This included the following steps: first using both the EPI and the T1 image the brain images were segmented using the unified segmentation algorithm implemented in SPM 8 (Wellcome Trust Center for Neuroimaging, 2009). The output of these procedures was the grey and white segmented brain images of each participant affine normalized to the MNI space. Then to optimize the spatial alignment of the images within the participants' sample, an average template was created using 6 iterations. The template image was then warped into Montreal Neurological Institute (MNI)

standard space. All the functional data was then warped using the above parameters into MNI space, and smoothed with a 9 mm Gaussian kernal to account for residual inter-individual differences and to take into consideration the assumptions of random field theory that is applied in family-wise error corrections (Worsley & Friston, 1995).

4.2.2.4.1 IGT

First-level analysis involved modelling single-subject BOLD responses in the design matrix which consisted of onset of stimulus trials which were card selections from either 'safe' decks (C and D), 'risky' decks (A & B), or motor control card decks, separately for each of the 4 blocks. Each event was modelled as 4 seconds event (see method), to capture the decision time and the output time. Two categorical parameteric modulations were also included to account for 1.) whether the card selection outcome was a 'win' (= +1) or 'lose' (= -1), and 2.) whether the card selection 'one trial before' was a 'win' or 'lose'. Trials where there was no card selection were excluded from the analysis and modelled as a separate regressor. Each condition was modelled by convolving delta functions of the regressors with a canonical hemodynamic response function.

To be able to generalize the results, few random effect analyses were conducted next. In all these analyses dependency between conditions and unequal variance between conditions were assumed. The focus was on results that survived family wise error correction at the cluster or peak levels, clusters that were part of the a-priori known regions (based on previous literature) that respond during the IGT. For completeness, results were presented with a threshold of p-value 0.001 (uncorrected) with at least 10 voxels per cluster

(the expected number of voxels per cluster by chance was 15). Voxel coordinates reported were based on standardized MNI space coordinate. Anatomical labelling was done using the Harvard-Oxford cortical and subcortical structural atlases as implemented in FSLview, part of (Smith et al., 2004).

The first analysis tested the general effects of conditions: the effect size of each of the conditions [(safe, risky, motor control) x 4 blocks] for each participant was used in a second level analysis. The following contrasts were used:

1.) Decision-making more than motor control trials, where all experimental trials (i.e. card selections from decks A, B, C, D) were compared to control trials (i.e. card selections from E, F, G, H).

2.) Card selections from risky decks (A & B) more than safe decks (C & D).

3.) Positive and negative linear change: linear modulation of BOLD response across all decks (A to D) for blocks 1 to 4 were weighted for a positive trend (i.e. starting from -2 to 2), as well as a negative trend (i.e. starting from 2 to -2), and this was compared with BOLD response from motor control trials for each participant before averaging scans of all participants.

4.) Type of deck and positive linear trend: interaction of BOLD response for trials when risky decks were selected more than for trials when safe decks were selected, and positive linear change (i.e. [risky > safe] x [positive change]). And interaction of BOLD response for trials when safe decks were selected more than for trials when risky decks were selected, and positive linear change (i.e. [safe > risky] x [positive change]).

The second analyses focused on neural correlates that directly predict the behavioural performance of the participants. The interest here was in the correlation between the learning effects observed of the BOLD and the behaviour. To conduct this analysis the interaction between selections (safe, risky) x block was computed per participant. Two learning windows were examined in separate models: early learning for comparing change in selection during block 1 vs. 2 (i.e. block 1: [1] safe > [-1] risky & block 2: [-1] safe < [1] risky); and overall learning comparing change in selection between all blocks (block 1: [2] safe > [-2] risky & block 2: [1]safe > [-1] risky & block 3: [-1] safe < [1] risky & block 4: [-2] safe < [2] risky). These contrast images were entered for a second level ANOVA in which the corresponding behavioural indices were modelled as covariates.

The analyses focused on the correlation of the performance learning rate with BOLD changes.

Third analyses examined the effects of the selection outcome as depended on the selected deck and the amount of experience with task. It was expected that as the learning occur responses to win or lose will change depending on the decks selected and hence the expectation of outcome from this selection. The effect size was computed for parametric modulation of the selection outcome parameters for each condition. Then linear change was computed for: interaction of BOLD response for lose more than win trials and blocks. Again this was computed for the early learning, block 1 vs. block 2 and overall learning for block 1 to 4.

Fourth analysis focused on how the outcome of the previous selection affected future decision processes. Here it was expected that the impact of win or lose independent of current selected deck will also change with time. To test that an analysis was conducted on

using the effect size computed for each condition (2 x 4) on the outcome one trial before. Specifically testing for positive and negative linear modulation of BOLD response for change in win and lose trials from one deck before for blocks 1 to 4 were weighted for a positive trend (i.e. starting from -2 to 2), as well as a negative trend (i.e. starting from 2 to -2).

Final analysis was based on examining how individual differences in responses to emotional stimuli, picture categorization based on valence (as index for their tendency to react emotionally), affected their learning rate at the neuronal level. For this analysis, each participant's neural responses to emotional pictures were computed.

4.2.2.4.2 Picture categorization task

First-level analysis consisted of modelling single-subject BOLD responses in the design matrix which included onset and duration (30 seconds) of each of the three emotional valence blocks, - positive, negative, or neutral images. Each condition was modelled by convolving delta functions of regressors with a canonical hemodynamic response function. The resulted images were then used in a second level analysis where subjects were treated as random variables. To test for regions that involve in processing the emotional property of these stimuli, the following comparisons were carried out: BOLD response of positive more than neutral images, as well as BOLD response of negative more than neutral images.

To assess the degree by which each individual activates emotional regions (e.g. amygdala) in response to an emotional stimulus, the activation levels of the amygdala was extracted (based on the group maxima, see results below) for each condition and for each

participant. From this were derived two indices: a negative index, computing amygdala response to negative vs. neutral; and a positive index, computing its response to positive vs. neutral. These two indices were then used as covariates in order to test the effects of amygdala general emotional reactivity on the IGT learning rate. It was hypothesized that emotional processes will have the largest impact on the early learning stage. Hence in the second level ANCOVA with the individual contrast interactions of early learning (change in safe vs. risky selection between block 1 and 2) with the two emotional-amygdala indices as covariates. The focus was on the modulation effects of the amygdala responses to negative, positive or to both (conjunction) on early learning.

4.3 Results

4.3.1 Learning on the IGT

Participants performed the motor control task with 96% mean accuracy, selecting the correct card deck as instructed on most trials. Analysis of behavioural performance across blocks of 20 card selections (Figure 4.3), using a repeated-measures ANOVA, found a significant effect of block ($F [3,75] = 4.79$, $p < 0.005$), which showed that participants learnt over time on the IGT. Further, within-subjects comparisons also showed that participants' performance on the IGT improved along a linear function ($F[1,25] = 10.95$, $p < 0.005$). On the behavioural performance index of final block minus first block, based on number of card selected from safe decks minus risky decks, participants total scores ranged from -7 to +19 (mean= 5.9; SD=7.05), and for the early learning index (second block minus first block) participants scores ranged from -4 to +21 (mean=3.15; SD=6.5), out of a possible range of -20 to +21. The varied performance levels across participants enabled a better comparison of learning and BOLD signal change in the fMRI data.

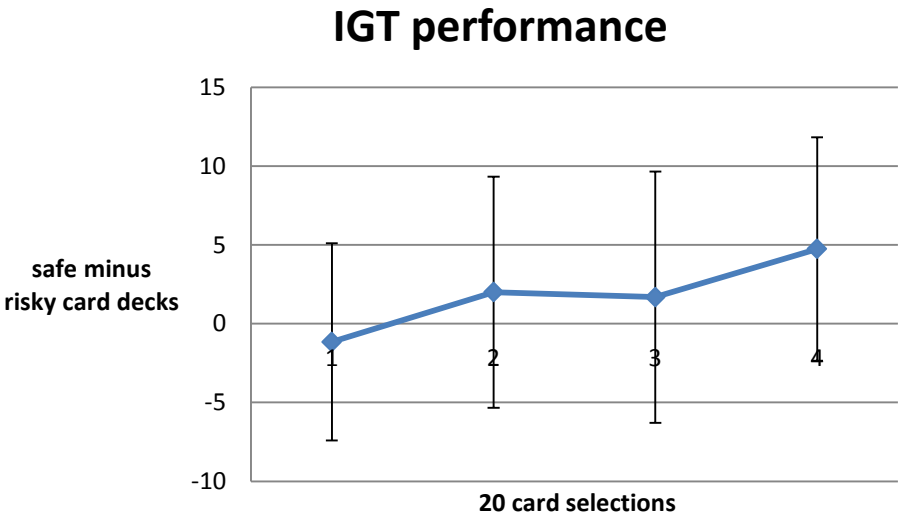


Figure 4.3 IGT performance over 4 blocks of 20 card selections for all participants

4.3.2 BOLD signal activation for decision-making minus motor control trials

BOLD response during card selection for contrast decision-making more than motor control trials on the IGT revealed several clusters that had significantly higher response for general decision-making in the left orbital frontal cortex, left occipital pole, left superior frontal gyrus, right anterior cingulate, right inferior frontal gyrus, right middle frontal gyrus, as well as the right superior parietal lobule, presented on Table 4.1 and Figure 4.4 Similar regions were also found to have significantly higher BOLD signal activation during card selection for general decision-making in the last block of the IGT more than the first block (red blob in Figure 4.5). Whole brain correlation of BOLD signal response for decision-making compared to motor control trials with the overall and early learning index (i.e. block 4 minus 1; block 2 minus 1) revealed no significant regions of activation for general decision making in the final block more than first block that was correlated with performance.

4.3.3 BOLD signal for decision making more than motor control which changed over time on the IGT

BOLD signal activation increased significantly across all blocks on the IGT in the left superior frontal gyrus (Table 4.1; yellow blob in Figure 4.6), while BOLD response decreased significantly across blocks in the left lateral occipital cortex, right occipital pole, left lingual gyrus (Figure 4.6).

Table 4.1 Brain regions which show a significant BOLD signal change for contrasts: decision-making minus motor control task, positive and negative linear changes over time on IGT.

Contrast	Brain region	Cluster size	X Y Z	t-value
Decision > Motor control	Left Orbital frontal cortex *	30	-15, 12, -15	4.78
	Left Occipital pole**	54	-12, -93, -9	4.63
	Left Superior frontal gyrus***	103	-6, 30, 45	4.16
	Right Anterior cingulate	37	6, 42, 15	4.06
	Right Inferior frontal gyrus***	110	45, 33, 15	3.90
	Right Middle frontal gyrus	14	39, 24, 42	3.61
	Right Superior parietal lobule	22	36, -51, 48	3.57
D > M, block 4 –block 1	(Same regions as contrast above)			
Positive linear change	Left Superior frontal gyrus	14	-21, 36, 48	3.50
Negative linear change	Left Lateral occipital cortex***	268	-30, -75, 18	4.53
	Right Occipital pole	38	15, -90, 27	3.71
	Left Lingual gyrus	11	-3, -84, 0	3.33

*FWE- corrected for peak level

** FDR– corrected at cluster level

*** FWE – corrected at cluster level

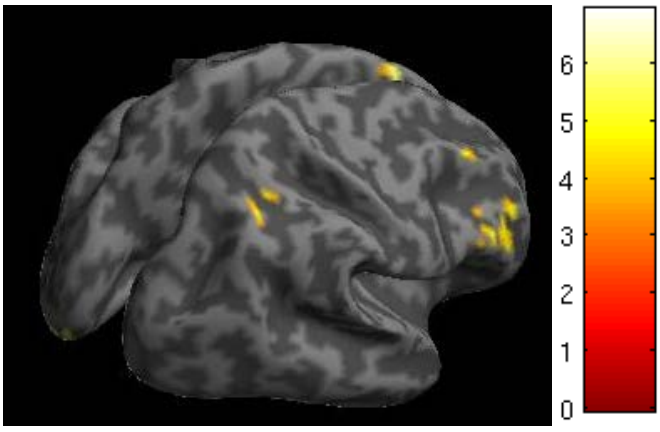


Figure 4.4 BOLD activation for decision making more than motor-control trials

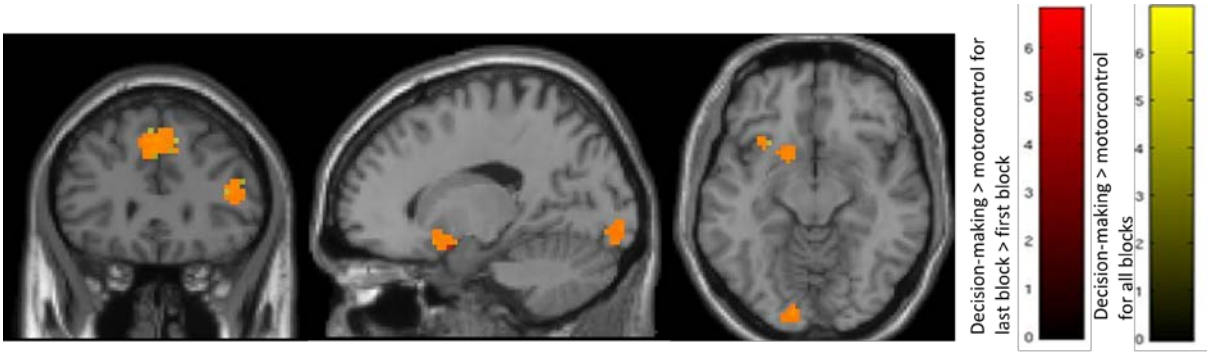


Figure 4.5 BOLD activation for decision-making more than motorcontrol trials for all blocks (yellow), and BOLD response for decision-making more than motorcontrol trials for block 4 versus block 1 (red). Overlaps are in orange.

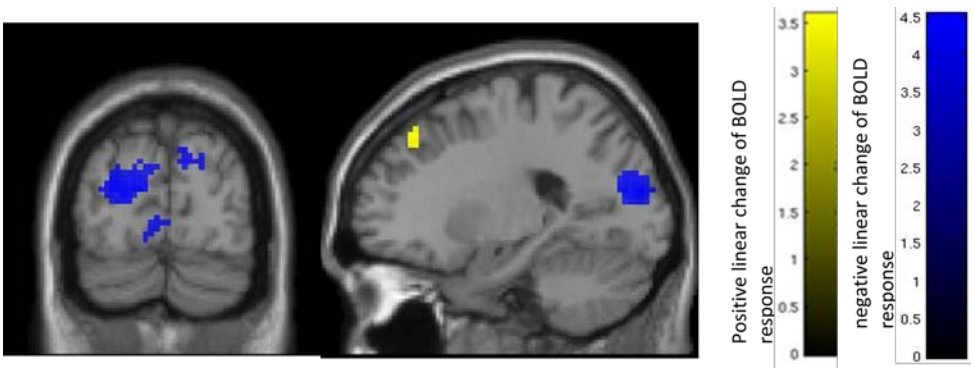


Figure 4.6 BOLD response for decision making more than motor control that was increasingly recruited across all blocks of the IGT (yellow) and BOLD activation for decision-making more than motor control that was decreasingly involved across all blocks (blue).

4.3.4 BOLD signal activation for risky compared to safe decks.

BOLD signal activation was significantly higher in the left supracalcarine cortex for risky compared to safe card decks, shown in Table 4.2. There was no significantly higher BOLD activation for safe more than risky card deck selections.

4.3.5 Interaction of BOLD signal response for contrast risky more than safe and positive change over time

An interaction of BOLD signal response for risky more than safe and positive change across all decks showed significantly higher activation in the left superior frontal gyrus and right planum temporale for risky more than safe card deck selections that increased over time (Table 4.2; red blob in Figure 4.7). For the interaction risky more than safe and positive change over blocks 1 and 2, significantly higher response was found in the left posterior cingulate and right inferior frontal gyrus for risky more than safe card deck selections which increased over the first to blocks only (Figure 4.8). No significant activation in any regions for risky more safe which decreased over time.

4.3.6 Interaction of BOLD signal activation for safe more than risky and positive change correlation with learning

The interaction of BOLD response for the contrast safe more than risky, and positive change over blocks 1 and 2, showed significantly higher activation in the left superior temporal gyrus for safe more than risky card deck selections which increased over the first and second blocks only (Table 4.2; yellow blob in Figure 4.7). No significant activation was found safe more than risky which increased across all blocks. There was also no significant activation for safe more than risky that decreased over time.

A whole brain correlation of BOLD response for safe more than risky contrast which changed positively over blocks 1 to 2 and learning index of block 2 minus block 1 showed

significantly higher activation in the right cerebellum, left frontal pole, and left caudate for safe more than risky which increased over the first half of the task that also predicted better learning on the early part of the IGT (Table 4.2; Figure 4.9). No significant activation was found for safe more than risky which increased over all blocks of the IGT that mirrored better performance.

4.3.7 One-before selection modulated BOLD response

BOLD response modulated by one-before card selection that changed positively over blocks revealed significantly higher activation in the right amygdala, right middle temporal gyrus, and right frontal orbital cortex to a previous win which increased over time (Table 4.2; Figure 4.10). The neural involvement was stronger for a previous win in the beginning of the IGT but shifted to a stronger activation to losses at the end of the task. This effect was independent of the current selected deck, suggesting that this was related to factors affecting decision-making processes rather than the decision itself. No significant neural response that was modulated by outcome of the current card deck selected was found.

Table 4.2 Interactions of BOLD signal change for risky or safe deck and positive or negative linear change, BOLD signal change for lose or win outcome and linear change, positive linear change of BOLD signal for lose or win one card before, and whole brain correlation with learning on the IGT.

Contrast	Brain region	Cluster size	X Y Z	t-value
Interactions:				
Risky > Safe	Left Supracalcarine cortex	32	-9, -87, 12	3.60
(risky > safe) x (positive change)				
Across all blocks	Left Superior frontal gyrus	21	-18, 21, 60	3.83
	Right Planum temporale	10	45, -33, 15	3.42
Block 1 and 2	Left Posterior cingulate	48	-3, -33, 24	3.89
	Right Inf. frontal gyrus	143*	54, 21, 15	3.83
(safe > risky) x (positive change)				
Block 1 and 2	Left Sup. temporal gyrus	14	-54, -18, -3	3.71
Positive correlation with learning:				
w. learning index block 2 minus block 1	Right Cerebellum (Crus I)	10	39, -45, -39	3.78
	Left Frontal pole	12	-30, 54, 21	3.70
	Left Caudate	10	-21, -3, 27	3.57
1 -before modulated response:				
Positive change over blocks	Right Amygdala**	57	36, 3, -21	4.86
	Right Middle temporal gyrus	17	63, -6, -15	3.81
	Right Orbital frontal cortex	13	39, 27, -21	3.70

*FWE- corrected at cluster level
** FWE- corrected at peak level

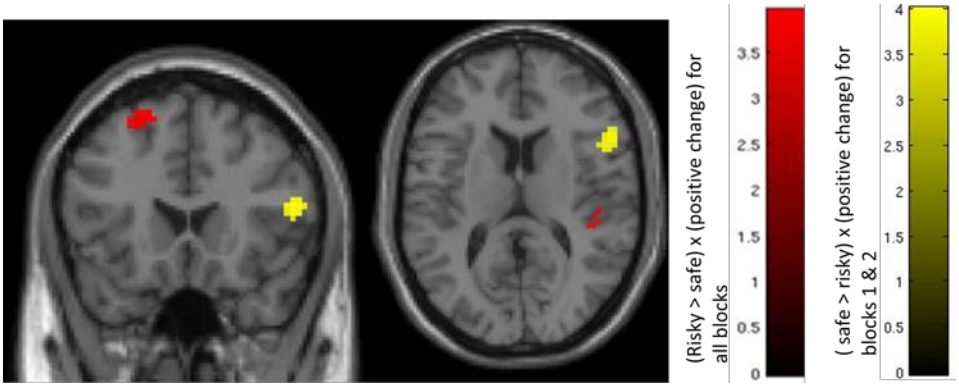


Figure 4.7 BOLD activation for risky > safe and positive change over all blocks (red), and safe > risky and positive change over block 1 to 2 (yellow).

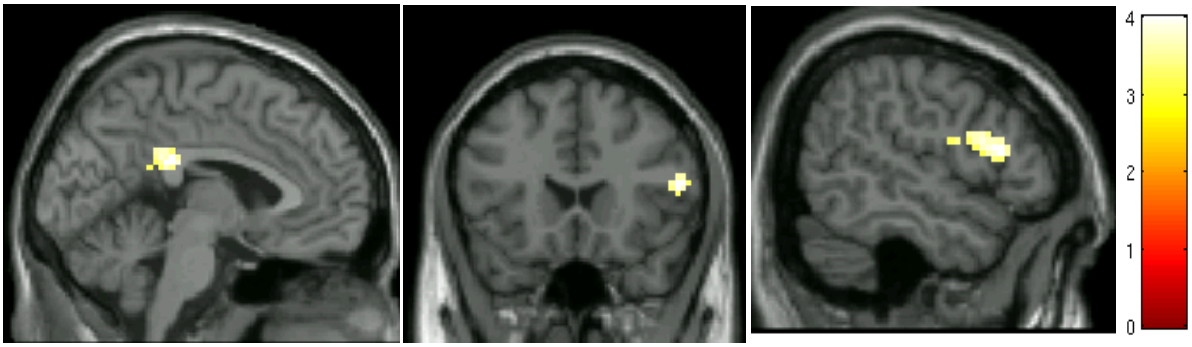


Figure 4.8 Interaction of BOLD signal for contrast risky > safe and positive change over block 1 to 2.

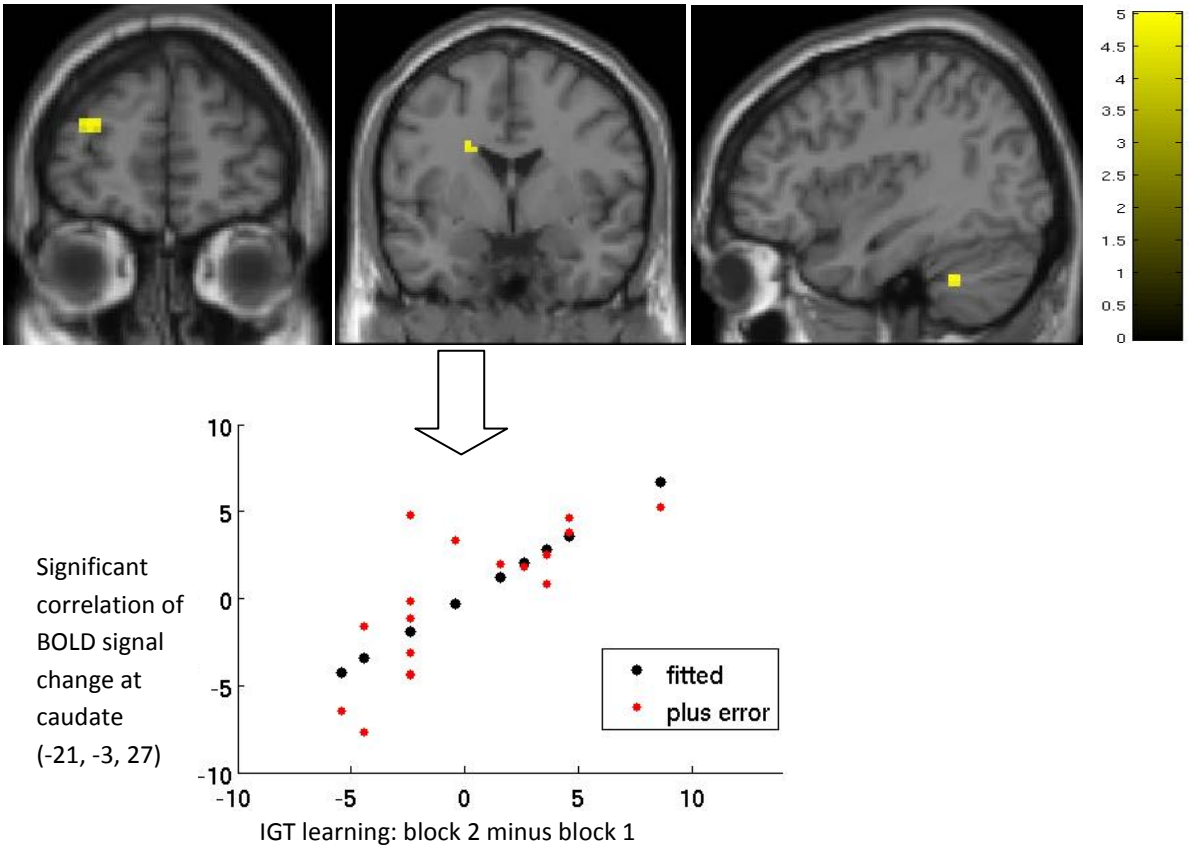


Figure 4.9 Whole brain correlations of neural regions for safe more than risky over block 1 and 2, with early learning performance on the IGT.

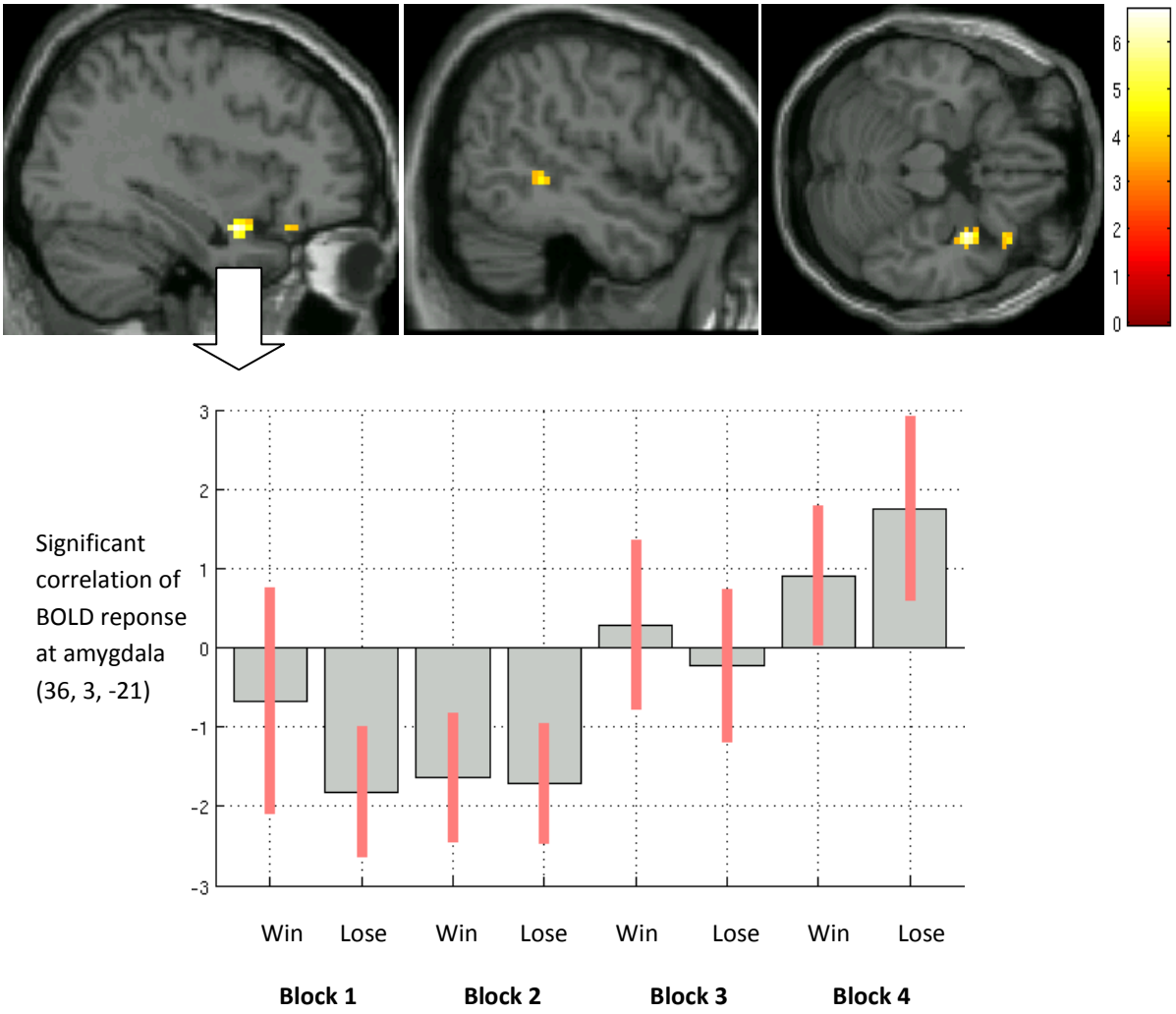


Figure 4.10 One-before modulated response: BOLD signal positive change across all blocks, and amygdala activation for win and lose over all 4 blocks.

4.3.8 BOLD response during the picture categorization and positive correlation with learning on IGT.

Contrast of BOLD response for positive more than neutral images showed significantly higher activation in the left occipital cortex, right lateral occipital cortex, right superior temporal gyrus, right frontal pole, and the right precuneus cortex for positively valence pictures compared to neutral images (Table 4.3; blue blob in Figure 4.11). For the

contrast of BOLD signal for negative more than neutral images reveal significantly higher activation in the left lateral occipital cortex, right inferior temporal gyrus, right amygdala, and right lateral occipital cortex for negatively valence images compared to neutral pictures (red blob in Figure 4.11). Further, the right amygdala region that responded to positive more than neutral images was also predictive of better learning in the first half of the IGT (Figure 4.12). The same region of the right amygdala which was more responsive to negative compared to neutral images was also associated with early learning on the IGT (Figure 4.13; Figure 4.14). A conjunction analysis of these two contrasts of BOLD response to emotional (positively and negatively valence) compared to neutral content images, with early learning performance on the IGT confirmed that the right amygdala responded more to both positive and negative emotional stimuli which also predicted of better learning in the early stages of the IGT (Figure 4.15).

Table 4.3 BOLD signal contrasts of positive more than neutral images and contrast of negative more than neutral images, with correlation to early learning index, as well as conjunction analysis of both contrasts correlated with early learning.

Contrast	Brain region	Cluster size	X Y Z	t-value
Positive > Neutral	Left Lateral Occipital cortex*	233	-51, -75, 15	4.93
	Right Lateral Occipital cortex**	213	51, -75, 3	4.45
	Right Superior Temporal gyrus	23	54, -6, -15	3.91
	Right Frontal pole	20	9, 57, 6	3.87
	Right Precuneus cortex**	83	6, -54, 21	3.81
Negative > Neutral	Left Lateral Occipital cortex**	225	-48, -66, 9	4.42
	Right Inf. Temporal gyrus	36	48, -57, -6	3.85
	Right Amygdala	15	27, -3, -12	3.63
	Right Lateral Occipital cortex	21	39, -66, 12	3.42
Positive correlation w. IGT performance block 2 – 1:				
Positive > neutral	Right Amygdala***	5	33, 6, -27	3.85
Negative > neutral	Right Amygdala***	1	39, -3 -24	3.14
Conjunction analysis:				
(positive> neutral)	Right Amygdala	13	39, -3, -24	4.38
x (IGT learning block 2 – block 1)				
and (negative> neutral)				
x (IGT learning block 2 – block 1)				

*FWE-corrected at peak level
** FWE- corrected at cluster level
*** under threshold level for number of voxels per cluster

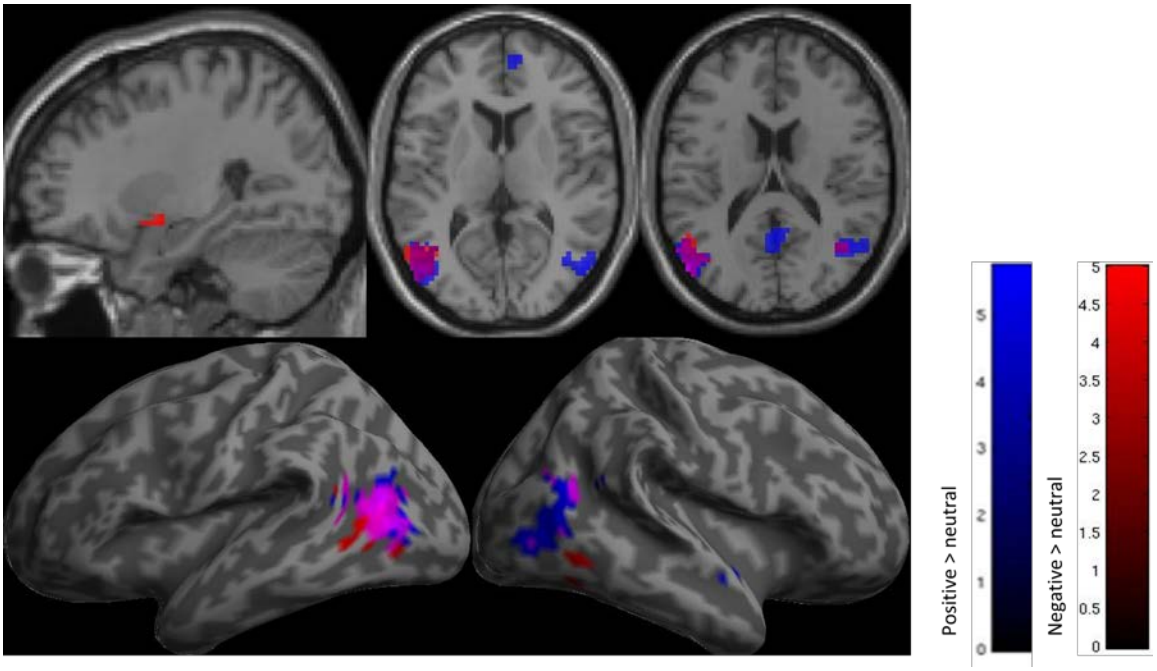


Figure 4.11 BOLD signal for the contrasts positive > neutral (blue) and negative > neutral (red). Overlaps are in pink.

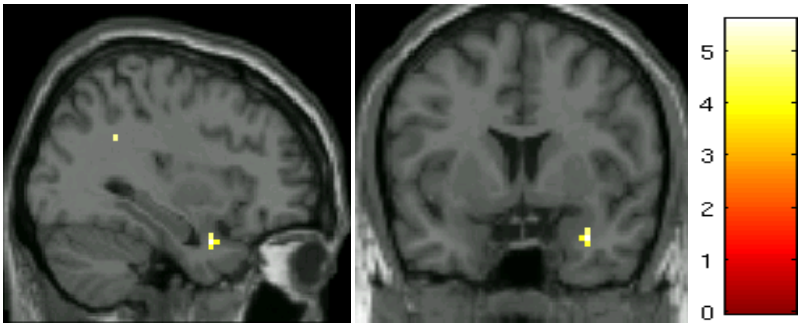


Figure 4.12 Whole brain correlation of BOLD response to positive more than neutral and early learning index on IGT: block 2 (safe – risky) – block 1 (safe – risky).

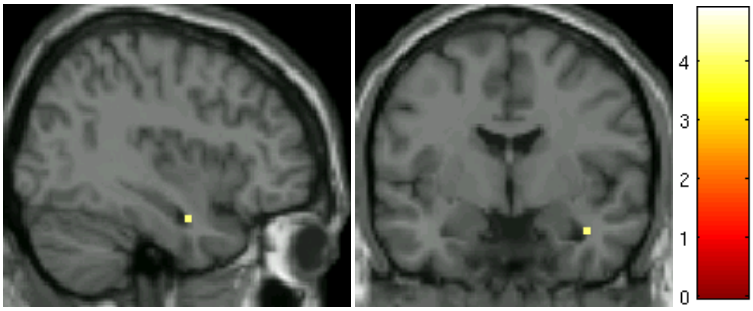


Figure 4.13 Whole brain correlation of BOLD response to negative more than neutral and learning index on IGT: block 2 (safe – risky) - block 1 (safe – risky).

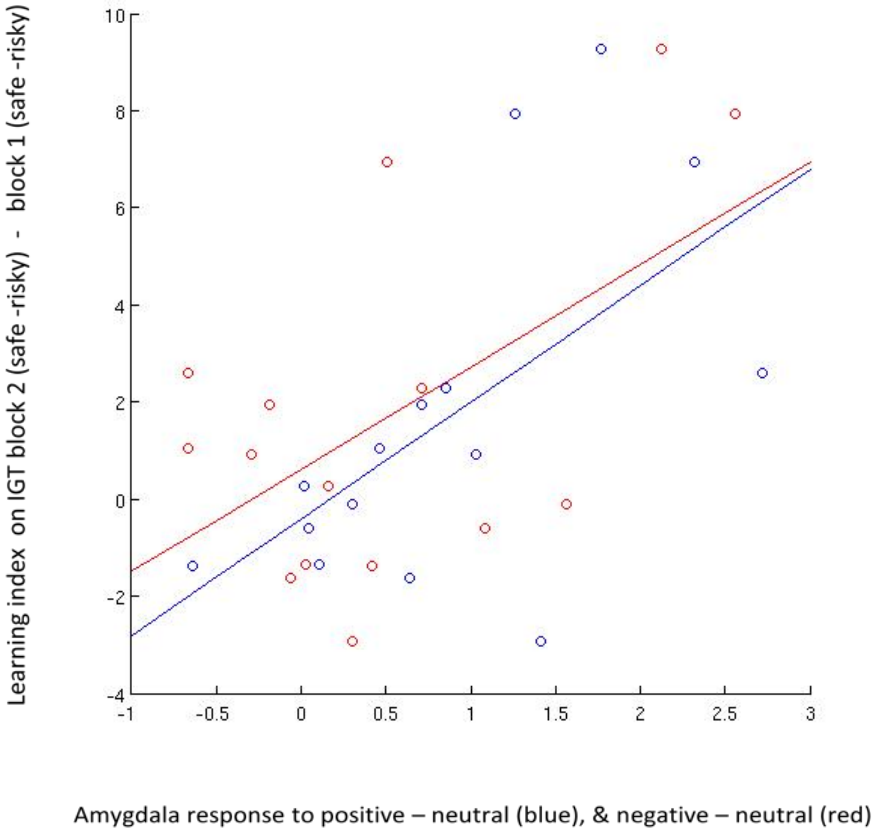


Figure 4.14 Amygdala response to positive minus neutral (blue)and negative minus neutral (red), with learning index on IGT for block 2 (safe – risky) – block 1 (safe – risky).

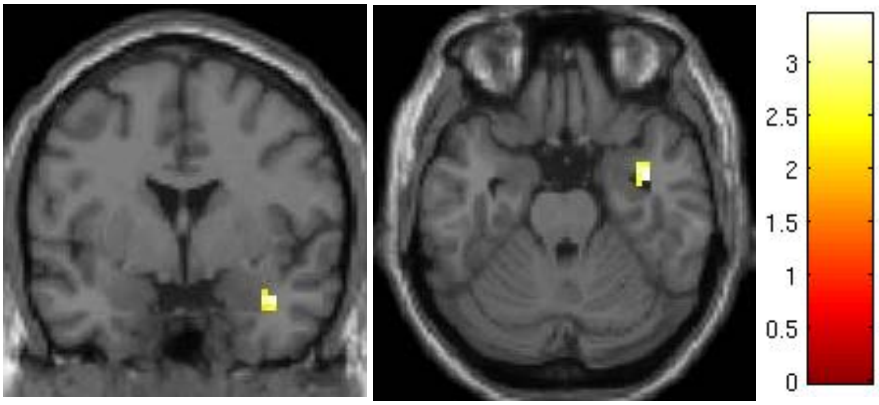


Figure 4.15 Conjunction analysis of interaction (positive> neutral) x (IGT learning block 2 – block 1) with interaction (negative> neutral) x (IGT learning block 2 – block 1).

4.4 Discussion

Overall and early learning on the IGT was achieved by participants in the study and BOLD response in neural regions related to decision-making compared to motor-control trials was also found. Repeated-measures ANOVA of number of safe compared to risky card deck selection across all blocks showed significant learning on the IGT along a linear function, and overall performance index of block 4 minus block 1 was a positive value which also indicated overall learning on the task. Early learning performance index of block 2 minus block 1 was above 0, suggesting that there was learning in the first half of the task. BOLD signal comparison showed significantly higher neural activity in the left OFC, right anterior cingulate, right middle frontal gyrus, left superior frontal gyrus, left visual cortex, right inferior frontal gyrus, and right superior parietal lobule for general decision-making more than motor control trials, which are similar to findings from a PET study (Ernst et al., 2002). These neural regions are also similar to those from neuropsychological studies with patients who have lesions in the vmPFC (Bechara et al., 1994; Bechara et al., 1996, Bechara, et al 2000) which are regions the SMH suggests to be involved in advantageous decision-making in the IGT (Damasio, 1994). Similar neural regions were also found for decision-making trials compared to motor control trials for the final block of the task compared to the beginning of the IGT. Further analysis to ascertain neural regions that increase and decrease over blocks on the IGT found that for a positive linear change across the task, the left superior frontal gyrus had significantly higher BOLD response. This suggest that the superior frontal gyrus which is a brain region related to working memory was the only region that linearly increased in activation across the whole task. For a negative linear regression of BOLD signal across the task showed only significant activity in the visual cortex,

suggesting that visual processes were decreasingly engaged in a linear fashion across the IGT. These finding suggest that SMH related neural regions are involved in decision-making trials compared to control trials in the IGT, however the recruitment of these regions do not change across the task.

BOLD signal contrasts between risky and safe card decks did not show any significant neural activation in areas mentioned in SMH, however analysis of the BOLD signal interactions for type of deck that is risky more than safe as well as safe more than risky examined in an interaction with linear change on the IGT showed significantly higher BOLD response in several brain regions. Significant BOLD activation in the left superior frontal gyrus was found for risky card selections compared to safe, which was increasingly involved across the entire IGT. Significantly higher BOLD signal in the posterior cingulate and inferior frontal gyrus was also found for risky more than safe card deck selections which were increasingly recruited in the first half of the IGT. This finding shows involvement of neural regions linked to working memory (Carlson et al., 1998) for risky more than safe card deck selection that are increasingly involved in the overall task and early stages of the IGT.

However differential neural regions were found for the comparison for safe more than risky card decks selection and positive linear change over the first and second blocks on the IGT. Significantly higher BOLD signal in the superior temporal gyrus was found for safe more than risky card deck selections which were increasingly recruited across the first half of the IGT. Whole brain correlation with early learning index showed significantly higher BOLD response in the left frontal pole, left caudate, and right cerebellum for safe compared to risky card deck selections which was increasing engaged over the early stages of the IGT. This finding differs from a previous study which found that the lateral OFC correlated with

selecting advantageously on the IGT (Lawrence et al., 2009), which is likely due to the difference in the type of performance measure used in the study by Lawrence and colleagues (2009) that was based only on total number of safe minus risky card deck selections. The current study used a performance index based on comparison between the second and first block of safe minus risky card selections to measure early learning performance on the IGT. Although comparisons involving the overall performance across the IGT did not reveal significant neural recruitment, the present study does reveal brain regions that are involved in selecting more from safe compared to risky card decks which are correlated with performance in the early phases of learning that increases over time, This finding strongly suggests that the frontal pole, caudate, and cerebellum are involved in early rule learning stages of the IGT such as the testing of possible rules which corroborates with the finding from chapter 3 of the current thesis of frontal pole and caudate involvement in early reward learning on the IGT.

Previous trial outcome modulated neural regions were also found. Significant BOLD response related to outcome of the previous card selection of trials was found in the right OFC, right amygdala, and middle temporal gyrus, which also linearly increased across all blocks of the IGT. This finding suggests that previous outcome of one trial before could have an influence on card deck selection which supports previous findings (Suzuki et al., 2003). The BOLD signal activation in the amygdala across the blocks in the IGT also showed an interesting pattern which suggested that this brain region was more responsive to wins at the beginning of the task but gradually switched to respond more to money losing trials by the last block of card selections. This shows that the amygdala was responsive to both rewards and losses on the IGT although this region was differentially involved across the

task. This suggests that valence of outcome plays a gradually different role on the IGT as the task progresses. This finding shows that the amygdala, OFC and temporal gyrus are involved in processing previous trial outcome which shifts from processing positive rewarding outcomes to negative reinforcements over the IGT.

Brain regions for emotional processes were also found for this group of participants which was associated with better learning on the IGT. Significant activity in the frontal pole, superior temporal gyrus, bilateral occipital cortex, and right precuneus cortex were found for classification of positive compared to neutral images. Significantly higher activity in the right amygdala, right inferior temporal gyrus, and bilateral occipital cortex was reported for categorization of negative more than neutral IAPS pictures. Further, whole brain correlation of the two previous BOLD comparisons with early learning index on the IGT revealed significant involvement of the right amygdala. Conjunction analysis of both previous comparisons showed the right amygdala confirmed that this region was significantly overlapped. This finding is different to a previous study which found that categorization of emotive pictures from the IAPS had significantly higher BOLD response in the vmPFC region which correlated with performance (Northoff et al 2006), however the study used net number of safe more than risky card selections as a performance measure which does not show improvement in selecting more advantageous card decks across the IGT. No significant neural regions were found for BOLD contrasts for emotion processing and overall learning performance which could be due to the small number of participants recruited in this study. These findings suggest that emotion valence related processes related to the amygdala are associated with learning in the early stages of the IGT.

Overall the finding suggest that neural regions previously suggested in the SMH to be involved in IGT performance is related to general decision-making rather than learning to make decisions that are advantageous based on outcome over time. Further the current study also shows that the involvement of the left frontal pole, caudate and cerebellum are predictive of improvements in reward learning i.e. learning from experience based on positive and negative outcomes from past decisions, and that the amygdala is also involved in emotional processes for both types of outcomes which also mirrors reward-based learning.

Chapter 5

General Discussion

5.1 Effects of age on IGT performance, emotion categorization, and apathy scale scores

The first study examined the effects of age on reward-based learning on the IGT, in relation to emotion related processes such as the categorization of emotive pictures according to valence and apathy related problems. Comparisons between the older and younger age groups' performance on the IGT, picture categorization and apathy scale scores showed no significant difference. However, there was a lack of correlations in the performance results of the older participant group unlike the younger controls. Only early performance on the IGT for the older participants was found to be positively associated with overall IGT performance. In the younger participants' results, a strong positive relationship was found between early and overall learning on the IGT. Both early and overall learning indices were also positively associated with positive rated IAPS images from the picture categorization task for the younger participants' group. Early learning on the IGT was also found to be negatively related to apathy scale scores based on the self-rated Apathy Evaluation Scale (Marin, Biedrzycki, & Firinciogullari, 1991). These findings show stronger associations between IGT performance and emotion related processes in younger participants compared to older participants, suggesting that age could have an influence on the relationship between emotion processes and reward learning abilities. However, these findings are based on correlational observations which limit the scope of interpretation. Experimental designs that examine directly the effect of emotion on reward learning ability in older and younger adults would be more informative of age effects on the relationship between emotion and reward-based learning.

There were also limitations to the sample of participants recruited. In both older and younger age groups, participants involved in the study were not a good representation of

different socio-economic backgrounds. Recruiting younger participants from an undergraduate psychology department which tends to have higher number of female students, meant that mostly mainstream educated younger female participants were involved in the study. Younger participants from different backgrounds such as those who have left formal education and are in full-time employment, or who are training on work-apprenticeship courses, as well as those without employment were not involved in this study. The encouragement to collect course credits as incentive for research participation also meant that like most psychological research, these findings on younger adults have been based on mainly undergraduate female participants. Older participants who took part in this study were retirees from more affluent backgrounds that tended to live nearby the university. Better incentives for taking part in research such as free advice on leading a healthy and active lifestyle, and better payment that covers travelling cost could encourage a wider group of older people to take part in future research.

The means of paying participants for their time and effort in the study were also different between the two groups of younger and older participants. This raises ethical concerns in regards to the difference in payment for both groups of people who took part in the study. Undergraduates recruited as younger participants were given course credits for an hour of participation however older adults taking part in the study were paid £6. This could also have had an effect on participants' motivation during the performance on the experimental tasks. Future studies should ensure that similar form of payment is given to all those who take part.

The findings from this study showed that age could have an effect on the relationship between reward learning and emotion processes, however further research

involving a wider representation of individuals from different educational and occupational backgrounds should be conducted so as to better understand the effects of age on reward-related learning and emotion processes, as well as how the relationship between these two abilities are changed due to age.

5.2 Differential systems in rule learning

The second study investigated how brain injured patients and healthy age matched controls performed on two different types of rule learning tasks that gave different forms of choice feedback: 1.) gains and losses accrued in the IGT and 2.) visuo-spatial location of a target in the Birmingham rule finding and switching task. There were no significant differences in the learning performance on the IGT and BRFS tasks between patients and healthy age-matched controls. This finding suggest that reward-based learning on the IGT is unimpaired in patients with brain injury, unlike previous studies which found patients with ventromedial prefrontal cortex (vmPFC) damage to be unable to select more advantageously on the similar task (Bechara et al., 1997; Bechara et al., 1999). A possible explanation could be that patients in the current study resemble the subset of patients in the study by Bechara and colleagues (1998) who had dorsolateral prefrontal cortex damage and were found to select more from advantageous card decks. Patients in this study were not recruited based on focal brain injury to particular neural regions. The widespread neural damage across all the patients recruited allowed for general comparisons with healthy age-matched control participants. However the interpretation of the results was limited by the overall small number of patients and control participants recruited. A higher number of patients and controls recruited would have improved the statistical power in the analysis and would have

allowed for the grouping of patients based on damage to different neural regions for comparisons between groups. These comparisons of performance on the IGT between different groups of brain injured patients with localized lesions would have allowed for a more focused investigation of possible effects of damage to specific brain regions on reward based learning as well as non reward-related rule learning.

In this study, patients' performance on the reward-based learning task (IGT), and general rule learning task (BRFS), were also examined in relation to categorization of emotive pictures, apathy, and executive function abilities. A positive relationship was found between overall reward learning on the IGT and number of IAPS images categorized as negative in emotion. This finding suggests that learning on the IGT in patients with brain injury could be linked to negative emotional experiences, such as learning from negative feedback on this task. Previous study on IGT performance and depression in high functioning adults has also showed a positive association between more advantageous card selections on the IGT and mild depression scale scores (Smoski et al., 2008). However, the correlational relationship limits the interpretation of a possible effect of negative emotions influencing reward learning on this task in brain injured patients. Further study to examine the effects of negative emotion on reward based learning in brain injured patient groups should be carried. Early learning performance index on the IGT was also found to have a positive association with immediate recall, a short-term memory test. This finding suggests that early reward-based learning in patients with brain injury is related to executive function abilities such as short-term memory, and this is unlike previous research which suggest that learning to select more from advantageous decks on the IGT is predicted by higher autonomic responses before disadvantageous card deck selections in healthy as well as

some subgroups of brain injured with no damage to vmPFC regions (Damasio, Adolphs, Damasio, 2003). A past study from the same group also suggested that executive function abilities to be dissociable from learning on the IGT (Bechara et al., 1998). However, the relationship between reward learning on the IGT and executive function abilities found in this study suggest that memory related abilities is linked to reward related learning in patients with brain injury. Further investigation of how impaired executive function ability in a larger patient group could have an effect on reward based learning should be carried out in comparison with healthy age-matched controls to ascertain the role executive function in reward-based learning.

5.3 Clinical assessment of apathy

The use of the self-rated versions of the Apathy Evaluation Scale (AES) and the informant's version of the AES could have resulted in less reliable findings of apathy related behaviour in the patients of this study. The lack of correlation found between the scores on the self-rated and informant's version of the AES is unlike previous research (Marin et al., 1991). The clinician's version of the AES could be a more reliable version to use in future studies with patient groups (Marin et al., 1991).

5.4 Voxel-based morphometry (VBM)

This patient study also mapped neural grey matter in correlation with behavioural performance on the two types of rule learning tasks, IGT and BRFS, which revealed similar as well as differential neural correlates for both tasks in patients with brain injury. VBM was

used to correlate grey matter damaged tissue with behavioural performance on both the IGT and BRFS, while controlling for age, education, emotion related processes, and executive function abilities. The right caudate was found to be significantly associated with early learning on the IGT, while the left frontal pole was revealed to be significantly related to non-reward based learning on the BRFS. A conjunction analysis also revealed that the left frontal pole was correlated to both performances on IGT and BRFS. This finding shows the neural correlates of learning in the early stages of the IGT which has not be found in any previous study using VBM regression analysis on patients' data. A previous study has instead reported that damage to the vmPFC to be significantly positively correlated with poorer performance on the IGT, in terms of total number of advantageous versus disadvantageous card deck selections (Gläscher et al., 2012). However, the previous study is not based on an overall comparison of changes in card deck selection from risky to safe card deck choices across stages of the task, or differences in card deck selections between middle and initial stages of the IGT (i.e. second and first block of the IGT), and therefore risks examining only emotion related neural regions related to a specific card deck type i.e. safe decks, such as the vmPFC, and not the neural region associated with reward-based learning such as the one shown in the current investigation to be the caudate. Further, the current study also found that less healthy tissue in the frontal pole was correlated with poorer performance on both the IGT and BRFS, suggesting that this brain region is involved in general rule learning related cognitive processes, such as executive function abilities in the exploratory and testing of rules, and could possibly be independent of reward related processes, such as emotional responses to validating gains and negative losses. Both types of rule learning involve a similar neural correlate in the left frontal pole as well as a differential neural association in the right caudate that is specifically linked to reward-based learning.

However, the use of a large number of covariates on the VBM analysis could have limited findings. A more controlled use of covariates to include only age, education, and apathy behavioural correlates could have been more informative of the neural regions associated with IGT and BRFS rule learning. The use of a large number of covariates in the analysis could have limited findings of other interesting brain regions associated with performance on both tasks, which could have been informative about the neural correlates of these different forms of rule learning and how they differed or were similar between these tasks.

In comparing the VBM findings from the current study to previous studies on neural regions linked to IGT performance which mainly involved the use of functional magnetic resonance imaging (fMRI), there could have been certain limitations since these two methodologies are operationalized by different measures. In this study neural correlates of patients with brain injury found to be associated with reward related and general rule learning were based on using grey matter volume estimations in the VBM analysis, however in the method of fMRI, hemodynamic responses of the brain during simultaneous task performance allows for comparisons between conditions to ascertain potential BOLD signal changes for particular contrasts. However, the use of different methodologies is important in research examining neural correlates of certain behavioural patterns in experimental tests. VBM allows for different questions to be asked such as how much damaged grey matter tissue in certain brain regions could explain impairments in a particular task, as well as to clarify claims from fMRI findings of neural correlates of a particular cognitive ability in healthy individuals. In this neuropsychological study, less healthy grey matter in similar neural regions reported in previous fMRI studies were found to be correlated with poorer performance on the similar reward learning tasks. This shows the importance in using

different methodologies in investigating a similar research question, such as the specificity of neural involvement in various cognitive abilities.

Overall, it was found in this study that patients with widespread neural damage were unimpaired on two types of rule learning tasks. The relationship between reward related rule learning and negative emotional experience, as well as short-term memory abilities, should be further examined to understand the direct effects of emotion and executive function abilities on reward-based learning. Neural correlates found in the caudate for reward related learning and the frontal pole for both forms of rule learning using VBM methodology should be further examined using other methods of neuroimaging such as fMRI, and recruiting larger numbers of patients with focal brain injury.

5.5 fMRI findings on healthy participants

In the third study, neural correlates involved during the performance of the IGT were investigated in a group of healthy participants who learnt to select more advantageously over trials on the task. Several questions and predictions were proposed:

1.) *Neural regions involved in IGT trials for general decision-making (i.e. selecting between card decks) compared to motorcontrol trials (with specified card decks to select from) may involve brain regions found previously using similar fMRI methods, such as the brain region of the vmPFC. And a further question of the possible increasing or decreasing neural involvement of these regions over blocks of 20 trials over the entire IGT was also examined.*

This study found that performance over the 4 blocks of 20 trials on the IGT for general decision-making compared to non-choice making trials, involved the left orbital frontal cortex, left occipital pole, left superior frontal gyrus, as well as the right hemisphere anterior cingulated, inferior frontal gyrus, middle frontal gyrus, and superior parietal lobule. Further, comparing the same contrast between block 4 and block 1 yielded the same neural regions. Comparisons of increasing or decreasing involvement of these regions over the blocks of trials showed only the left superior frontal gyrus to be increasingly recruited over blocks of the IGT, while only visual cortex regions were significantly less involved across blocks of the task.

Neural regions such as the left orbital frontal cortex (OFC), right anterior cingulate, and right middle frontal gyrus, was suggested to be involved in the selection from advantageous card decks on the IGT (Bechara, Damasio & Damasio, 2000a). However, whole brain correlations with IGT learning performance scores in the current study did not show the recruitment of these brain regions in learning across the IGT. These findings suggest that brain regions such as the vmPFC are linked to a general decision-making ability that is differentiated from learning on the IGT. Working memory related brain region, the superior frontal gyrus (Carlson, Martinkauppi, Rämä, Salli, Korvenoja, Aronen, 1998) was increasingly recruited over card selections on the IGT, as well as a decreasing involvement of the visual cortex was also found across the entire task.

2.) *Neural regions recruited for type of card deck selected (i.e. safe more than risky decks) and increase over time overall on the task (i.e. interaction of time and cards selected) was examined. And the question whether a whole brain correlation of BOLD signal from these contrasts with learning performance IGT would show the involvement of medial frontal gyrus, frontal pole, dlPFC, anterior cingulate, amygdala, insula, thalamus, caudate, and cerebellum was examined. Further, would an interaction of card deck type (i.e. safe more than risky decks) and increase over the first half of the IGT (i.e. positive linear change for block 1 to 2), correlated with learning over the first half of the task (i.e. block 2 minus 1) involve similar neural regions?*

Left superior temporal gyrus was recruited in selecting from safe card decks compared to risky card deck selections increasingly over the first half of the IGT which could be linked to the processing of emotional stimuli such as facial expressions (Bigler, Mortensen, Neeley, Ozonoff, Krasny, Johnson, et al., 2007) which was used on the computerized version of the IGT to denote a win (happy) or loss (sad) on the every trial. In the whole brain correlation of BOLD response for this contrast with learning performance on the IGT, the right cerebellum, left frontal pole, and left caudate was found to be involved in learning on the first half of the IGT. This supports the finding from the second study of this thesis based on patients with brain injury which showed that the frontal pole and caudate are associated with reward based learning on the IGT.

3.) *Neural correlates for type of card deck selected (i.e. risky more than safe decks) and increase over the entire IGT as well as during the first half of task may involve*

the anterior cingulate, medial frontal cortex, and insula which was found in a previous fMRI study using the same version of the IGT (Lawrence et al., 2009).

The current study did not find any neural regions related to the SMH for the comparison of risky more than safe card deck selections. Only the left supracalcarine cortex was found to be recruited for risky more than safe card deck selections, which could be explained by the participants' visual attention on the visual cues that accompanied the reward and losses outcome of each card selection for risky more than safe card deck choices (e.g. sad face; Dichter, Felder, Bodfish, Sikich, & Belger, 2009). This finding is unlike the study by Lawrence and colleagues (2009) which reported the anterior cingulate, medial frontal cortex, insula, as well as visual cortex to be associated with risky more than safe choices. These different findings could be due the individual differences in reward based learning patterns. The group of participants from the previous study by Lawrence and colleagues (2009) could have recruited more of an avoidance strategy towards losses, which is supported by the lack of significant BOLD signal changes found for the safe more than risky card deck trials. Individual differences in strategies used for reward based learning on the IGT should be further investigated in terms of differences in neural correlates that are associated with various possible approaches of learning on this task.

4.) *This study also investigated neural regions associated with response modulation of outcome for one trial before, that could have been increasingly recruited over blocks of the IGT. Brain regions which may be involved are the amygdala and*

orbital frontal cortex. Based on the SMH, patients with lesions in the vmPFC, which is an area situated medially on the OFC, and the amygdala have impaired ability to recruit emotion feedback for decision-making on card decks (Bechara, et al., 1997; Bechara, et al., 1999).

This study found the involvement of the right amygdala, right orbital frontal cortex, and right middle temporal gyrus for response modulation of one trial before. The finding supports previous claims from Damasio's team that the vmPFC and amygdala is recruited during performance on the IGT (Bechara et al., 1999), however the current finding does not support the claim from the SMH which posits that 'anticipatory' processes before a card selection determines better performance. Instead, the neural regions of the OFC and amygdala are more likely to be recruited in response to the outcome of feedback from the previous trial which has an influence on choice of card deck. This also supports previous findings by Suzuki and colleagues (2003), based on SCRs recorded after outcome of each card selection trial which was found to be correlated with learning performance across blocks on the entire IGT. Hence, the claim made by Damasio and colleagues in the SMH, that the amygdala and OFC are recruited for the evaluation of choices before a card selection that determines whether a safe or risky card deck is selected, lacks valid support. Since both behavioural/physiological as well as fMRI based evidence suggests that the amygdala and OFC are associated with outcome evaluation processes rather than a decision-making process before a card selection.

5.) *Neural regions associated with emotion processes for categorization of pictures with emotive content, based on pleasantness, unpleasantness, or neutral feeling of the image, was investigated for the same group of participants recruited. The prediction was that neural regions involved in emotion related processes in this sample of healthy adults would be similar to brain regions recruited during reward based learning on the IGT. Neural regions involved in the processing of positive or negative emotion evoked in the picture categorization task was also investigated on whether they were similar to the brain regions associated with learning performance on the IGT?*

The neural regions of the lateral occipital cortex, right frontal pole, right precuneus cortex, and right superior temporal gyrus were associated with categorizing positive versus neutral IAPS images. The lateral occipital cortex, right inferior temporal gyrus, and right amygdala were also found for classification of negative compared to neutral IAPS pictures. Whole brain correlations with learning performance on the IGT showed that participants' right amygdala recruited for categorization of positive as well as negative emotional pictures was also associated with better learning on the IGT in the first 40 trials of the IGT. This finding supports the claim from the SMH that the amygdala is associated with performance on the IGT. However it is still unclear as to the exact role that this brain region plays in learning to select advantageously on the IGT, except that an emotional component does factor into reward based learning on the task, such as the processing/evaluation of outcome of card selections for subsequent trials.

Overall the fMRI findings show that neural regions such as the left OFC, left occipital pole, left superior frontal gyrus, right anterior cingulated, right inferior frontal gyrus, right middle frontal gyrus, and superior parietal lobule are involved in general decision-making, which is not associated with learning performance (i.e. more advantageous card selections in the final compared to initial stages of the task). However, neural regions in the right cerebellum, left frontal pole, and left caudate were found to be involved in learning performance on the first half of the IGT. This finding supported neuropsychological evidence of frontal pole and caudate involvement in learning to select advantageously over the stages of the IGT. The vmPFC and amygdala were found to be recruited for processing of outcome response for a previous trial, and the amygdala which was also found to be involved in processing emotional content of emotive pictures of the same group of individuals was also correlated with learning performance on the IGT.

5.6 Implications on SMH

The SMH which is based on evidence from the IGT has been inadequate to show that learning (i.e. the gradual improvement) over trials on the IGT is influenced by an 'anticipation' time period just before making a card selection. The vmPFC was suggested to be directly involved in these evaluative processes of choices that take place during the anticipation/evaluation before a card selection, and the amygdala was reported to be recruited in outcome responses after each card selection (Bechara et al., 1999). In the current study, the neural regions of the OFC and amygdala were found to play a role in the emotional processes of outcome responses, however only the amygdala was also found to be associated with reward learning the IGT. Choice from each card selection was not found

to modulate these neural regions suggesting that it is unlikely that the OFC was recruited for cognitive processes involved in evaluation choices before making a choice on the IGT. This finding supports previous evidence that SCRs for outcome of card selection was significantly associated with learning (i.e. significant improvement) over trials on the IGT (Suzuki et al., 2003). The evidence that the amygdala was recruited in processing both positive and negative emotions and associated with better performance on the IGT in the first 40 trials for the same group of individuals, also suggests that emotional experience (i.e. validating or negative) from outcome of one card selection before plays a role in the subsequent card selection that follows, therefore playing a direct role in decision-making on the IGT.

5.7 Strengths and limitations

The modified version of the IGT used in this study was effective examining behavioural and neural correlates of reward-based learning. More associations between IGT learning performance and emotion related processes such as categorization of emotive IAPS images for younger participants was found unlike the lack of similar relationships in the results for older age group participants, which suggest potential age effects on the relationship between emotion processes and reward-based learning. Interesting findings based on patients' performance showed that widespread neural tissue damage did not impair learning on the IGT. Categorizing of negative emotional pictures was also found to be linked to better learning on the IGT. Immediate recall ability was also shown to be related to improvements on IGT performance. Neural correlates of the frontal pole and caudate was found in be associated with learning on the IGT for patients' data based on VBM, as well as findings from fMRI results from healthy participants. The increased statistical power of two

card decks for each of the risky and safe decks, with the same contingencies of wins and losses, would have been a reason for these findings. The use of the learning performance index which took into account the number of safe compared to risky card decks for the final versus the first 20 card selections on the IGT was necessary to indicate how performance had improved over the task.

Sample groups used in the studies were small and could have resulted in lower statistical power in the analysis. Recruitment of patients, older individuals, as well as younger adults should also include a wider representation of the different social and economic backgrounds, and better incentives could be used to encourage participation. Patients recruited for the neuropsychological study had widespread neural damage, however focal lesion research could help in ascertaining potential differences in terms of behavioural and neural correlates between groups of people with different regions of neural damage to shed further light on specificity of neural mechanisms in reward related learning and emotion based processes.

Use of an emotion categorization task to show a potential relationship between reward-based learning and negative emotions in patients groups, as well as positive emotions in younger adults, was limited. Emotion processes examined by the categorization task used in this study was based on emotional feeling evoked by the pictures from the IAPS. However, the feeling of winning and losing money on the IGT is qualitatively different from the emotions experienced on the picture categorization task. On the IGT, the feedback from outcome of card selections involves excitability (whether one is gaining or losing money overall on the task), whereas the picture categorization task depends on subjective emotions evoked by the object or scene in the picture from the IAPS. There are limitations

in interpreting the relationship between emotion processes of these two tasks. Physiological measure of reactivity such as SCRs would have been a better means of ascertaining somatic responses to wins and losses on the IGT.

The correlational design of these studies has been useful in ascertain potential relationships between reward learning and emotional processes as well as executive function ability, however this design limits the interpretation of the directional relations between these processes. An experimental design that examines how an emotional cue would directly improve or pamper reward learning, would enable a directional interpretation of the effects of emotion on reward-based learning. In the patient study, comparisons between patients with focal lesions in different brain regions on executive function ability and reward related learning, would be give better indication of how different neural regions and executive function play a role in learning based on feedback.

The use of different methodologies, VBM and fMRI, has been complementary in providing evidence of similar neural involvement of frontal and caudate neural regions in reward-based learning. VBM based on patients' data to examine the regions of damage neural tissue and the effects on task performance, and fMRI involving healthy participants to examine neural correlates during performance, showed clearly similar neural recruitment of the frontal pole and caudate for reward-based learning for two sample groups. The use of an additional class of brain tissue in the modified segmentation procedure has improved VBM methodology for examining the specificity of damaged tissue and the association with poorer performance in experimental tasks for patients with various forms of brain injury as recruited in this study. Future studies should use different methodologies in ascertaining neural involvement in task performance for reward related learning abilities.

5.8 General conclusion

The studies carried out to investigate the behavioural and neural correlates of reward-based learning on the IGT has shown that emotion processes and executive function abilities are linked to learning based on reward feedback, as well as the association of neural regions such as the frontal pole, caudate, and amygdala in reward learning. The different sample groups used in the studies conducted showed that there is a possible effect of age on the relationship between emotion processes and reward-based learning that seems to be lacking in older adults. In the patient group with different aetiologies, the interesting finding that could help in understanding how learning is related to emotion was the association found between negative emotion processes and performance in reward learning, suggesting that an avoidance of losses could have been used for learning. The relationship found between executive function ability and reward learning also suggests that immediate recall abilities could be involved in learning that requires evaluating feedback and the application to future trials. Using VBM, neural correlates for reward related learning based on patients' data was found in the frontal pole and caudate, while general non reward-based learning was associated only with frontal pole neural region, suggesting a differential neural region for reward related learning in the caudate and a similar brain region of the frontal pole for both forms of rule learning. The fMRI study carried out involving healthy participants also showed similar neural regions to be recruited for reward related learning. The frontal pole and caudate was found to be involved in learning on the IGT, and brain regions previously associated with IGT performance the vmPFC was shown to be recruited for the processes related to outcome response. The amygdala was also found to be recruited for emotion processes in the same group of participants, which was associated with better reward

learning on the IGT. Overall the studies have contributed towards further understanding of possible effects of age on the relationship between emotion and reward learning, as well as the use of different methodologies in investigating neural correlates of reward based learning.

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Appendices

Appendix 1. Instructions for IGT

1. Instructions for Practice task

First of all we are going to do a practice task. On the screen in front of you, you will see 4 decks of cards labelled E, F, G and H. After a few seconds, a message will appear asking you to pick a card from one of these decks (e.g. “Pick Card E”). After seeing this message, you should press one of the 4 buttons to select the correct deck. Be aware that you only have 3 seconds to click on the deck. If you respond too slowly, a message will appear telling you that you are “Too Late”. Try and click on the correct deck as quickly as possible after seeing the message.

2. Instructions for real task

We are now going to start the real task.

To begin with, you will see the same 4 decks of cards; E, F, G and H. I want you to do exactly the same thing as you just did during the practice task. After a few trials, the decks will change and you will see 4 new decks of cards on the screen. These decks will be labelled A, B, C and D. After a few seconds, a message will appear that asks you to pick a card. As in the practice task, you will then have 3 seconds to click on one of the decks of cards. This time, however, it will be up to you to decide which deck you pick a card from.

Every time you pick a card from deck A, B, C or D, the computer will tell you that you have won some money. I don’t know how much money you will win, you’ll find out as you go along. Every time you win, the green bar at the bottom of the screen gets bigger.

Every so often, however, when you pick a card, the computer will tell you that you have lost some money. I don't know when or how much you will lose, you will find out as you go along. Every time you lose, the green bar at the bottom of the screen gets smaller.

You are absolutely free to switch from one deck to the other at any time, and as often as you wish.

The goal of the game is to win as much money as possible and, if you find yourself unable to win, make sure you avoid losing money as much as possible.

You won't know when the game will end. You must keep on playing until the computer stops.

I am going to give you this £2000 credit, as seen on the green bar at the bottom of the screen, to start the game. The red bar at the bottom of the screen is a reminder of how much money you borrowed to play the game, and how much money you have to pay back before we see how much you won or lost.

It is important to know that the computer does not make you lose money at random. However, there is no way for you to figure out when or why you lose money. All I can say is that you may find yourself losing money on all of the decks, but some decks will make you lose more than others. Even if you lost a lot of money, you can still win if you stay away from the worst decks.

Appendix 2.

Apathy Evaluation Scale (self-rated)

Name: _____ Date: __/__/__

For each statement, circle the answer that best describes your thoughts, feelings, and activity in the past 4 weeks.

1. I am interested in things.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
4	3	2	1

2. I get things done during the day.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
4	3	2	1

3. Getting things started on my own is important to me.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
4	3	2	1

4. I am interested in having new experiences.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
4	3	2	1

5. I am interested in learning new things.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
4	3	2	1

6. I put little effort into anything.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
1	2	3	4

7. I approach life with intensity.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
4	3	2	1

8. Seeing a job through to the end is important to me.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
4	3	2	1

9. I spend time doing things that interest me.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
4	3	2	1

10. Someone has to tell me what to do each day.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
1	2	3	4

11. I am less concern about my problems than I should be.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
1	2	3	4

12. I have friends.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
4	3	2	1

13. Getting together with friends is important to me.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
4	3	2	1

14. When something good happens, I get excited.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
4	3	2	1

15. I have an accurate understanding of my problems.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
4	3	2	1

16. Getting things done during the day is important to me.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
4	3	2	1

17. I have initiative.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
4	3	2	1

18. I have motivation.

NOT AT ALL	SLIGHTLY	SOMEWHAT	A LOT
4	3	2	1

Appendix 3. LARS: instructions and items

-Instructions for administration of the Lille Apathy Rating Scale –

The Lille Apathy Rating Scale (LARS) comprises 33 queries belonging to nine domains, each corresponding to a clinical manifestation of apathy. The interview is structured and the questions should to be posed exactly as stated. To obtain the best validity, it is not advisable to change the vocabulary or to add additional comments to the questions. Before beginning the interview, the patient has to be instructed as follows: "*I am going to ask you some questions about your daily life. It is important that you base your answers on your life over the last four weeks*" If the patient evokes general events or any that predate the last month, he or she must be reminded that only the current situation must be referred to: "*Please try to answer according to your current way of life, by referring to the last four weeks*" A precise scoring mode is proposed for each reply and should be followed as closely as possible. When an item does not apply to the patient, it is scored "0", for non-applicable (NA). When the reply is not clear at all and cannot be classified, it is also scored "0" for a non-classifiable reply. The scale's overall score ranges from –36 to +36

-Lille Apathy Rating Scale –

1. Everyday productivity -What do you do during the day? Tell me about your day-to-day life.

Time taken to reply[1]

no reply	2
reply after prompting	1
spontaneous reply but only after some time	0
immediate reply, one activity mentioned without hesitation	-1
immediate reply, several activities mentioned without hesitation	-2

Number and variety of activities mentioned

none	2
one activity but prompting needed to obtain another	1
several activities mentioned	0
detailed organisation of a typical day but every day follows the same schedule.	-1
detailed organisation of a typical day but the reply shows that the activities change according to the day of the week or the time of year (for example housework, going to the cinema, watching TV, gardening, visiting friends, etc.)	-2

2. Interests -What are you interested in? What do you like doing to keep yourself occupied?

The delay must reflect a deficit in or absence of reactivity from the subject. Delays due to speaking or wordfinding difficulties should not be considered when scoring these items

Time taken to reply

no reply	2
reply after prompting	1
spontaneous reply but only after some time	0
immediate reply, one activity mentioned without hesitation	-1
immediate reply, several activities mentioned without hesitation	-2

Number of activities mentioned

none or only one	1
several	0
regrets having to choose between so many activities	-1

-How many times a week do you …(*do the first hobby or pastime mentioned above*)?

Less than once a week	1
Once or several times a week	0
Regrets not being able to devote more time to the activity	-1

3. Taking the initiative -In general, do you decide to do things or does someone have to push you a little?

I have to be pushed	1
N.A. Non-classifiable reply	0
I decide to do things myself	-1

-When you have to go to an appointment, a meeting or a formal occasion, do you have to be told to get yourself ready?

I need to be told	1
N.A. Non-classifiable reply	0
I get ready spontaneously	-1

-When you have to make an appointment (for example with the doctor or dentist), do you do it yourself or do you wait for someone to do it for you?

I wait for someone to do it for me	1
N.A. Non-classifiable reply	0
I do it myself	-1

-Do you take part spontaneously in daily living activities or do you need to be asked?

I have to be asked	1
N.A. Non-classifiable reply	0
I take part spontaneously	-1

4. Novelty seeking -Do you like finding out about something new (a new TV programme or a new book)?

No, that doesn't interest me	1
N.A. Non-classifiable reply	0
Yes, that interests me	-1

-Do you like trying out new products, tools or recipes that you're not familiar with?

No, that doesn't interest me	1
N.A. Non-classifiable reply	0
Yes, I like trying things I'm not familiar with	-1

-Do you like visiting places you've never been to before?

No, that doesn't interest me	1
N.A. Non-classifiable reply	0
Yes, I like visiting places I've never been to before	-1

-When you go out for a drive or when you're travelling by train or bus, do you enjoy looking at the countryside, the houses?

No, that doesn't interest me	1
N.A. Non-classifiable reply	0
Yes, I like to see if anything has changed	-1

5. Motivation -Voluntary actions -When you decide to do something, are you easily able to make an effort or is it difficult?

I find it difficult to make an effort	1
N.A. Non-classifiable reply	0
I can easily make an effort	-1

-When you don't manage to do something, do you try to find other solutions?

No, I give up	1
N.A. Non-classifiable reply	0
Yes, I try again	-1

-When you decide to do something, do you see it through to the end or do you tend to give up?

I tend to give up (I am easily discouraged)	1
N.A. Non-classifiable reply	0
I see it through to the end	-1

-When you can't find something (for example a document or an object), do you go to a lot of trouble looking for it?

No, if I don't find it quickly, I stop looking	1
N.A. Non-classifiable reply	0
Yes, I keep looking until I find it	-1

6. Emotional responses -When you watch a film, do you easily become emotional or moved?

No, I don't experience any particular emotion	1
N.A. Non-classifiable reply	0
Yes, I am easily moved	-1

-When someone tells you a joke or when you watch a comedy sketch on TV, do you laugh easily?

No, I don't experience any particular emotion	1
N.A. Non-classifiable reply	0
Yes, it makes me laugh	-1

-Do you feel happy when you hear some good news?

No, I don't experience any particular emotion	1
N.A. Non-classifiable reply	0
Yes, I'm happy	-1

-Do you feel sad when you hear some bad news?

No, I don't experience any particular emotion	1
N.A. Non-classifiable reply	0
Yes, I'm sad, it worries me	-1

7. Concern -When you have a problem (for example when your TV set breaks down), does it worry you?

No	1
N.A. Non-classifiable reply	0
Yes, I worry easily	-1

-When something's not working or when something unexpected happens, do you think about finding a solution?

No, I give up	1
N.A. Non-classifiable reply	0
Yes, I look for a solution	-1

-When your partner or children have a minor problem (when they're ill, for example), does that concern you, do you worry about them?

No, I don't feel very concerned about that	1
N.A. Non-classifiable reply	0
Yes, I worry.	-1

-Do you like to ask how your family and friends are on a regular basis?

No, often I wait until someone tells me how they are	1
N.A. Non-classifiable reply	0
Yes, I often ask them how they are (I phone them, etc).	-1

8. Social life

-Do you have friends?

No, not many or I don't see them any more	1
N.A. Non-classifiable reply	0
Yes, and having friends matters a lot to me	-1

-When you meet friends, do you enjoy spending time with them or it is a chore?

It's a chore	1
N.A. Non-classifiable reply	0
I enjoy it	-1

-In conversation, do you start talking or do the others tend to speak to you first?

I only talk if someone starts talking to me	1
N.A. Non-classifiable reply	0
I start talking with no prompting	-1

-During a discussion, do you give your own opinion spontaneously or do you fall into line with someone else's opinion?

I tend to fall into line with someone else's opinion	1
N.A. Non-classifiable reply	0
I give my own opinion spontaneously	-1

9. Self-awareness -When you've finished doing something, do you take stock of the situation and think about what is going well and what's not?

No, I don't think about the end result	1
N.A. Non-classifiable reply	0
Yes, I take stock of the situation	-1

-After having taken a decision, do you sometimes think that you've made the wrong choice?

No, I'm happy with the choice I make	1
N.A. Non-classifiable reply	0
Yes, I sometimes regret having made certain choices	-1

-When you've been unpleasant to someone, do you sometimes feel guilty afterwards?

No, I don't care	1
N.A. Non-classifiable reply	0
Yes, I'm ashamed of myself	-1

-If, during a discussion, you realize that you're in the wrong, are you able to admit it -at least to yourself?

No, I don't admit that I'm in the wrong	1
N.A. Non-classifiable reply	0
Yes, I admit it.	-1

Total score	/36

Appendix 4. Informant's version of the Apathy evaluation scale

Name:_____ Date:_____

Informant's name:_____ Relationship:_____

For each statement, circle the answer that best describes the subject's thoughts, feelings, and activity in the past 4 weeks.

He is interested in things
Not at all Slightly Somewhat A lot

He gets things done during the day
Not at all Slightly Somewhat A lot

Getting things started on his own is important to him
Not at all Slightly Somewhat A lot

He is interested in having new experiences
Not at all Slightly Somewhat A lot

He is interested in learning new things
Not at all Slightly Somewhat A lot

He puts little effort into anything
Not at all Slightly Somewhat A lot

He approaches life with intensity
Not at all Slightly Somewhat A lot

Seeing a job through to the end is important to him
Not at all Slightly Somewhat A lot

He spends time doing things that interest him
Not at all Slightly Somewhat A lot

Someone has to tell him what to do each day
Not at all Slightly Somewhat A lot

He is less concern about his problems than he should be
Not at all Slightly Somewhat A lot

He has friends
Not at all Slightly Somewhat A lot

Getting together with friends is important to him
Not at all Slightly Somewhat A lot

When something good happens, he gets excited
Not at all Slightly Somewhat A lot

He has an accurate understanding of his problems
Not at all Slightly Somewhat A lot

Getting things done during the day is important to him

Not at all	Slightly	Somewhat	A lot

He has initiative

Not at all	Slightly	Somewhat	A lot

He has motivation

Not at all	Slightly	Somewhat	A lot